CLINICAL STUDY PROTOCOL V132_01EXP Version 1

A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine in Healthy Adults (18-45 years of age)

EUDRACT No. 2014-002430-31

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5.3.1 Subject Diary Reminder, Safety Follow-up and/or Post-vaccination Blood

PROTOCOL SYNOPSIS V132_01EXP

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
Novartis Pharma Services AG	V132_01EXP	MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and Meningococcal C-CRM$_{197}$ Conjugate Vaccine
Title of Study: A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine in Healthy Adults (18-45 years of age)		
Study Period: Approximately 12 months for each subject		**Clinical Phase:** Phase 1

Background and Rationale:

Neisseria meningitidis (*N. meningitides*)serogroup C (MenC) is one of the major serogroups causing invasive meningococcal disease. Case fatality in Germany has ranged between 6% and 8% between 1999 and 2006, and has remained generally consistent across the different European countries, varying between 6-11%, with the case fatality rate being notably higher for serogroup C disease than for serogroup B. The safety and immunogenicity of the Novartis Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) has been confirmed through years of commercial use. For children over the age of 12 months, for adolescents and for adults a single dose is recommended. For infants between 2 and 12 months of age, the recommended schedule for primary immunization with the Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) is two doses given with an interval of at least 2 months, followed by a booster. (Novartis Meningococcal C-CRM$_{197}$ Conjugate Vaccine Investigator Brochure).

A more potent Meningococcal C-CRM$_{197}$ Conjugate Vaccine formulation might enable a reduction of the antigen dosage and/or a reduction in the number of doses needed in infants. One approach to achieve more potent well-characterized sub-unit vaccines - like the Novartis Meningococcal C-CRM$_{197}$ Conjugate Vaccine - is the use of new adjuvants that activate Toll-like receptors (TLRs).

Novartis is developing a small molecule immune potentiator (SMIP) LHD153 that targets TLR7. The objective driving the development of LHD153 is to achieve a vaccine adjuvant with strong immunopotentiating properties and minimal side effects. In line with this objective, it has been postulated that the ideal SMIP should remain local and target innate immune cells at the injection site. To this end, LHD153 contains a

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functional phosphonate group to allow for adsorption to aluminum hydroxide. The arginine salt derivative of this compound is LHD153R. Preclinical results from animal models for bacterial and viral antigens, including MenC, MenB, rabies, HIV and respiratory syncytial virus (RSV) showed increased functional antibodies and antigenspecific T-cells with LHD153R adsorbed to aluminum hydroxide (aluminium hydroxide/LHD153R) when compared to aluminum hydroxide adjuvanted controls. *In vitro* toxicity screens confirmed that LHD153R is not phototoxic, genotoxic or mutagenic. Furthermore, toxicology studies in dog and rats showed that intramuscular (IM) injection of aluminum hydroxide/LHD153R was well tolerated. Importantly, in contrast to free LHD153R, toxicokinetic analysis in rats and dogs confirmed very limited exposure of LHD153R when adsorbed to aluminum hydroxide after IM injection.

The aim of this Phase 1 clinical study is to assess the safety of aluminium hydroxide/LHD153R adjuvanted MenC-CRM$_{197}$ conjugate vaccine (MenCCRM$_{197}$/Aluminium Hydroxide/LHD153R) and to compare the antibody-mediated immune response elicited by MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R with the licensed aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®). Furthermore, a comprehensive set of exploratory objectives has been selected to assess the systemic exposure of LHD153 after intramuscular injection of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R, to evaluate the quality of the specific immune response against MenC-CRM$_{197}$ in detail and to evaluate biomarkers that may be predictive of safety and/or innate immune activation

The licensed Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) has been selected as the primary vaccine candidate to assess the safety and immunopotentiating properties of aluminium hydroxide/LHD153R for several reasons. Firstly, the safety and immunogenicity profiles of the Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) have been well established through years of commercial use. Secondly, a more potent MenC-CRM$_{197}$ conjugate vaccine might enable a reduction of the antigen dosage or the number of doses needed in infants. Finally, the MenC-CRM$_{197}$ conjugate is a well-characterized, single antigen preparation which provides an ideal setting to compare the potential of this new aluminium hydroxide/LHD153R adjuvant.

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Study Objectives:

Primary Safety Objective:

To assess the safety of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R as compared to that of aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine.

Primary Immunogenicity Objective:

To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine at Day 29, as measured by human complement serum bactericidal assay (hSBA) directed against *N. meningitidis* serogroup C.

Secondary Immunogenicity Objectives:

1. To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal CCRM$_{197}$ Conjugate Vaccine, at Day 8 and Day 181 after vaccination, as measured by hSBA directed against *N. meningitidis* serogroup C. Baseline antibody titers will also be measured by hSBA.
2. To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal CCRM$_{197}$ Conjugate Vaccine at Day 8, Day 29 and Day 181 after vaccination, as measured by an enzyme-linked immunosorbent assay (ELISA) to *N. meningitidis* serogroup C. Baseline antibody concentrations will also be measured by ELISA.

Exploratory Objectives:

1. To evaluate the systemic exposure of LHD153 at several early time-points after IM injection of MenC-CRM197/Aluminium Hydroxide/LHD153R or aluminium hydroxide adjuvanted Meningococcal C-CRM197 Conjugate Vaccine.
2. To explore the frequency of B cells specific for Men C polysaccharide and CRM$_{197}$ protein at baseline (Day 1) and at Day 8, Day 29 and Day 181 after vaccination with

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MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R or the aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine. Subsequently, the B cell repertoire of the antigen specific B cells and the specific antibody functionality will be analyzed in a selected subset of subjects.

3. To explore the baseline T cell mediated immunity to CRM$_{197}$ and to evaluate the frequency and quality of CRM$_{197}$ specific T cells induced by MenC-CRM$_{197}$/Aluminium Hydroxide/ LHD153R compared to aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine at Day 8 and Day 29.
4. To evaluate biomarkers that may be predictive for safety and/ or innate immune activation.

Study Design:

This Phase 1, randomized, observer-blind, dosage-escalation study will be performed at a single center. In total, approximately 80 healthy male and healthy non-pregnant female adults (18-45 years of age) will be enrolled in the study. Subjects will be randomized to receive a single IM vaccination of either the licensed aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine (i.e. 10 µg MenC conjugated to CRM$_{197}$, adjuvanted with 1 mg aluminium hydroxide) or one of four dosages of the investigational vaccine, MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R (i.e. 10 µg MenC conjugated to CRM$_{197,}$ adjuvanted with 1 mg aluminium hydroxide and one of four dosages [12.5, 25, 50 or 100 µg] of LHD153R)

For the dosage-escalation of LHD153R, the subjects will be enrolled into 1 of 4 cohorts, in a stepwise manner with 20 subjects per cohort. Subjects in all cohorts will be randomized in a 1:4 ratio, to receive either aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine (control) or MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R with increasing doses of LHD153R.Cohort 1 will receive 12.5 µg of LHD153R; Cohort 2 will receive 25 µg of LHD153R; Cohort 3 will receive 50 µg of LHD 153; and Cohort 4 will receive 100 µg of LHD153R (Table 1).

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Table 1. Subjects Randomized per Cohort and Treatment Dose Group

Cohort	Group	Subjects/ Group	MenC Dosage* (µg)	Adjuvant Dosages		Total Volume/Dose	Total Subjects/Group
				Aluminium Hydroxide (mg)	LHD153R (µg)		
1	A	4	10	1	0	0.5 mL	20
	B	16	10	1	12.5	0.5 mL	
2	A	4	10	1	0	0.5 mL	20
	C	16	10	1	25	0.5 mL	
3	A	4	10	1	0	0.5 mL	20
	D	16	10	1	50	0.5 mL	
4	A	4	10	1	0	0.5 mL	20
	E	16	10	1	100	0.5 mL	

*Conjugated to 12.5-25 µg CRM_{197}

After vaccination, all subjects will be confined to the clinical site for 24 hours for clinical observation and blood sampling for exploratory endpoint measurements.

Importantly, all cohorts will have a staggered entry.

- For each cohort, the first 5 subjects (i.e. the first 1:4 randomization block) to receive either aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (n=1) or MenC-CRM_{197}/Aluminium Hydroxide/LHD153R (n=4) will be treated at a vaccination rate of 1 subject each day.
- After entry of the first 5 subjects in each cohort, the enrollment will be paused. The remaining 15 subjects for each cohort will be enrolled only after DMC review of the safety results obtained through Day 15 has been finalized (Table 2).
- Furthermore, after entry of all 20 subjects in each cohort, enrollment will be paused again.Enrollment of the first 5 subjects in the next cohort will only proceed after the Day 29 safety results of the previous cohort have been reviewed by the Data Monitoring Committee (DMC) (Table 2).

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Table 2. Overview of staggered entry of subjects for each cohort

Cohort	1st Stage of enrollment	MenC-CRM197/ Aluminium Hydroxide	MenC-CRM197/ Aluminium Hydroxide /LHD153R	2nd Stage of enrollment	MenC-CRM197/ Aluminium Hydroxide	MenC-CRM197/ Aluminium Hydroxide /LHD153R
1	First 5 subjects with vaccination rate of 1 subject/day	1	4	Remaining 15 subjects, after DMC review of Day 15 safety results	3	12
2		1	4		3	12
3		1	4		3	12
4		1	4		3	12

The DMC review after the first 5 subjects of each cohort and in between the cohorts will be performed according to predefined stopping/pausing guidelines used to ensure the safety of study subjects. These stopping/pausing guidelines are based on FDA guidance and with grading scales from the CBER Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials". See protocol section 3.6 for further details.

Safety Measurements

Schedule of safety data collection:

- Solicited local and systemic adverse events (AEs), body temperature and all unsolicited AEs will be collected until Day 15.
- All serious adverse events (SAEs), medically attended AEs, AEs leading to study withdrawal, new onset of chronic disease (NOCDs), and adverse events of special interest (AESIs) will be collected from the date of signed informed consent to study completion at Day 366.
- All concomitant medications administered in relation to the reported AEs will be collected from vaccination to study completion at Day 366.

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Solicited local AEs include injection site erythema, injection site induration, injection site pain and injection site swelling. Solicited systemic AEs include body temperature ≥ 38.0°C (as measured orally), loss of appetite, nausea, fatigue, generalized myalgia, generalized arthralgia, headache, chills, vomiting, diarrhea, generalized rash and urticaria.

All AESIs will be reported in the same manner as SAEs. All AEs will be monitored until resolution or, if the AE becomes chronic, a cause is identified. If an AE is unresolved at the conclusion of the study, a clinical assessment will be made by the investigator and the medical monitor to determine whether or not continued follow-up of the AE is warranted.

The relationship of the study treatment to any AE will be determined by the investigator as probably related, possibly related, or not related; the relationship of the study treatment to any SAE will be determined by the investigator as probably related/suspected, or not related.

Safety Laboratory Parameters

To assess laboratory AEs, blood and urine samples will be collected from each subject as outlined in Table 3 to perform blood chemistry, hematology, and urine analyses.

Safety laboratory samples will be drawn from all subjects at pre-vaccination screening (between Day -21 and Day -3) at Day 1 (pre-vaccination), at Day 8 and at Day 29. Safety laboratory assessments will include sodium, potassium, bicarbonate, blood urea nitrogen, creatinine, liver function tests (ALT, AST), a complete blood count and Creactive protein. A urine sample will be collected at the same time-points and will be assessed for the presence of protein, glucose and red blood cells.

Primary and Secondary Immunogenicity Measurements

Four blood samples per subject (i.e. at Day 1, Day 8, Day 29 and Day 181) will be collected for serum preparation and determination of antibody-mediated immune responses to MenC-CRM$_{197}$ as outlined in Table 3 and Table 4. See section 7.3 for further details.

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Exploratory Measurements

In all subjects who agree by signing a separate Informed Consent, additional blood samples will be collected at Day 1, Day 4, Day 8, Day 29 and Day 181 for exploratory assays. The purpose of these assays is to assess the systemic exposure of LHD153, to determine the frequency and quality of B- and T-cells specific for MenC polysaccharide and/or CRM$_{197}$ and to evaluate biomarkers that may be predictive of safety and/or innate immune activation. Subsequently, MenC-CRM$_{197}$ specific B-cell repertoires as well as the MenC-CRM$_{197}$ specific antibody functionalities will be analyzed in a selected subset of subjects, dependent on the results from primary and secondary immunogenicity measurements and the volume of whole blood (specific B cell repertoire) and serum (specific antibody functionality) remaining for additional testing. See section 7.4 for further details. All exploratory analyses may be performed after the Clinical Study Report (CSR) has been completed, in which case these data will be submitted as an addendum to the CSR.

Number of Subjects planned:

Approximately 80 adult subjects will be randomized, with anticipated dropout rates of 5% by Day 181 (last serology time point), and 10%, by Day 366 (last safety time point).

Sample size is not driven by statistical assumptions for formal hypothesis testing, but the proposed number of subjects will be sufficient to provide a descriptive summary of the safety and immunogenicity of the study vaccine.

Study Population and Subject Characteristics:

Healthy adult male and female volunteers between 18-45 years of age, inclusive.

The list of inclusion and exclusion criteria is included in protocol section 4.0, Selection of Study Population.

Study Vaccines:

The MenC-CRM$_{197}$ conjugate is a lyophilized powder consisting of 10 µg of Men C polysaccharide conjugated to 12.5-25 µg CRM$_{197}$ carrier protein. The MenC-CRM$_{197}$ lyophilized powder will be reconstituted with adjuvant by the unblinded designated site

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staff member who is to follow the procedure as described in the vaccine preparation instructions in the Investigator Site File (i.e. the vaccine will be prepared in the clinic prior to administration).

The lyophilized Men-CRM$_{197}$ powder will be reconstituted with either:

(a) aluminium hydroxide adjuvant

(b) aluminium hydroxide/LHD153R adjuvant with specified dosages of LHD153R (12.5, 25, 50 and 100 µg)

The components for each formulation of MenC-CRM$_{197}$ will be provided in a separate kit, together with detailed instructions for reconstitution and dilution steps.

Aluminium hydroxide/LHD153R with specified dosages of LHD153R will be prepared by dilution of the highest aluminium hydroxide/LHD153R dosage (100 µg of LHD153R) with aluminium hydroxide.

In each cohort, subjects will be randomized to receive one injection of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R adjuvant or aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine. The 0.5 mL of vaccine will be injected IM in the deltoid muscle, with preference that the injection is administered in the nondominant arm.

Primary Endpoints:

Safety Endpoint(s):
Safety will be assessed by measuring the frequency of local and systemic solicited AEs, unsolicited AEs, SAEs, AESIs, NOCDs, and safety laboratory data for all subjects. Specifically,

- The frequency and percentage of subjects with solicited local and systemic AEs through Day 15. Time intervals after vaccination that will be summarized are: 30 min post-vaccination, Days 1-4 (without 30 min), Days 5-8, Days 8-15, Days 1-8 (without 30 min) and Days 1-15 (without 30 min).
- The frequency and percentage of subjects with any unsolicited AEs from the day of

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vaccination (Day 1) to Day 15.

- The frequency and percentage of subjects with SAEs, medically attended AEs, AEs leading to study withdrawal, NOCDs, AESIs for the following time periods: day of signed informed consent until study completion (Day 366), day of vaccination (Day 1) to Day 29 and Day 29 to study completion (Day 366).
- The absolute values and changes in hematology, chemistry, and urinalysis parameters.
- The frequency and percentage of subjects with abnormal laboratory parameter values as classified by investigator normal ranges (low, normal, high) and as classified by CBER toxicity grading scales, when available.

Primary Immunogenicity Endpoints:

Geometric mean titers (GMTs) measured by hSBA directed against *N. meningitidis* serogroup C from samples collected on Day 1 (baseline, before vaccination) and Day 29 as well as the GMR of the titers (Day 29 / Day 1).

Secondary Immunogenicity Endpoint(s):

- GMTs and corresponding GMRs measured by hSBA directed against *N. meningitidis* serogroup C for samples collected at Day 8 and Day181.
- Percentage of subjects with hSBA seroresponse at Day 8, Day 29, and Day 181. seroresponse is defined as a post vaccination hSBA ≥8 for subjects with a baseline hSBA <4 or have an increase of at least 4 times the baseline hSBA level for subjects with pre-vaccination hSBA ≥4.
- Antibody geometric mean concentrations (GMCs) against *N. meningitidis* serogroup C measured by ELISA for samples collected on Day 1 (baseline, prior to vaccination), Day 8, Day 29 and Day 181.
- The percentage of subjects with at least a 4-fold increase in antibody concentrations to *N. meningitidis* serogroup C measured by ELISA on Day 8, Day 29 and Day 181 relative to baseline (Day 1).

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Exploratory Endpoint(s):

Testing and analyses of exploratory endpoints may be performed after the Clinical Study Report (CSR) has been completed, in which case these data will be submitted as an addendum to the CSR.

1. Serum concentration of LHD153 at Day 1 baseline (prior to vaccination), Day 1 (1h , 2h, 4h, 8h and 24h after vaccination) and Day 4 by LC-MS/MS.
2. Frequency of meningococcal C polysaccharide-specific and CRM$_{197}$-specific B cells at Day 1 (baseline), Day 8, Day 29 and Day 181 by ELISPOT.
3. Diversity of the meningococcal C polysaccharide-specific B-cell repertoire at Day 1 (baseline), Day 8, Day 29, and Day 181 by immunoglobulin cDNA sequencing.
4. Functionality of antigen specific antibodies will be assessed at Day 1 (baseline), Day 8, Day 29 and Day 181 by analysis of immunoglobulin isotype, glycosylation state and their ability to fix complement, promote antibody-dependent cell mediated cytoxicity, induce phagocytosis and activate FcR+ cells. If the quantity of serum available for this specific exploratory objective is limited, assessments of isotype, glycosylation state and complement fixing capacity will be prioritized over the other assessments.
5. Frequency and quality of T cells specific for CRM$_{197}$ at Day 1 (baseline), Day 8 and Day 29 by fluorescence activated cell sorting (FACS) analysis using intracellular staining with a wide panel of cytokines and surface markers to identify cell populations.
6. Serum concentrations of a panel of 30 chemokines and cytokines at Day 1 (baseline), Day 1 (6h and 24h after vaccination), Day 4 and Day 8 by multiplex Electro-chemoluminescence based assay.
7. Gene expression profile in whole blood at Day 1 (baseline), Day 1 (6h and 24h after vaccination), Day 4 and Day 8 by RNA micro array analysis.

Statistical Analyses:

The study is exploratory in nature, thus analyses will be descriptive and no formal hypothesis testing will be performed.

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Primary Safety Analyses

The primary safety analyses will be based on the safety set for solicited and unsolicited adverse events. There is no statistical null hypothesis associated with the safety objective, which will be analyzed descriptively.

Immunogenicity Analyses

The primary immunogenicity analyses will be based on the per-protocol set (PPS) on Day 29. The primary analyses will also be performed using the Full Analysis Set (FAS) as a measure of the sensitivity/robustness of the results. All other immunogenicity assessments will be performed using the PPS or the appropriate subset of subjects. The antibody concentrations/titers will be summarized using GMC/GMTs and two-sided 95% confidence intervals (CIs) constructed by exponentiation (base 10) of the least square means of the logarithmically transformed (base 10) antibody titer. The 95% CIs will be obtained from an analysis of covariance (ANCOVA) with baseline concentration/titer as a covariate. Additional details will be further described in the statistical analysis plan.

The immunogenicity endpoints based on subjects meeting criteria for seroconversion or achieving a certain threshold value will be summarized using frequencies and percentages and associated two-sided 95% Clopper-Pearson CIs. For analyses of seroconversion, separate summaries may be provided based on seropositivity status at baseline.

Interim Analysis: An Interim Analysis will be performed on the immunogenicity and safety data collected from all subjects until Day 29 after all cohorts have been enrolled. Further details regarding the interim analysis are contained in section 8.6.
Data Monitoring Committee: A Data Monitoring Committee (DMC) will be implemented to review safety data during scheduled periodic reviews. The DMC will review safety data collected until Day 15, as described in the DMC charter and in the statistical analysis plan, after enrollment of the

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first 5 subjects in each cohort, before proceeding with enrollment of the remaining subjects in each cohort. In addition, the DMC will review safety data collected until Day 29 after enrollment for each cohort. Enrollment of subjects in subsequent cohorts will only proceed after the DMC review is completed. The same enrollment sequence will be utilized for each cohort. Further information regarding the DMC is discussed in more detail in the protocol, section 3.7, Data Monitoring Committee.		

Table 3: Time and Events Table – Treatment Period (until Day 29)

	Visit Type	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit	Phone Call	Clinic Visit
	Study Day	**-21 to -3**	**1**	**4**	**8**	**15**	**22**	**29**
	Visit Window (Days)	**n/a**	**n/a**	**n/a**	**-1/+1**	**-1/+1**	**n/a**	**-2/+2**
	Visit Number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**
Study Event	**References**							
Study Treatment								
Vaccination	Section 5.2		X					
Screening and Safety								
Informed Consent	Section 5.1.1	X						
Demographic Data & Medical History	Sections 5.1.2	X						
Physical Exam	Sections 5.1.2 and 5.2.1	X	X[a]					
Safety Laboratory blood draw (10 ml)	Section 7.1.7	X	X[a]		X			X
Urinalysis	Sections 3.5	X	X[a]		X			X
Pregnancy Test	Sections 5.1.2 and 5.2.1	X	X[a]					
Exclusion/Inclusion Criteria	Section 4.0	X	X[a]					
Randomization	Section 5.2.3		X[a]					
30 Minutes Post Injection Assessment	Section 5.2.6		X					
Subject Diary Dispensed with Training	Section 5.2.6		X					
Subject Diary Reminder	Section 5.2.6			X	X			

Subject Diary Reviewed and Collected	Section 5.3.1					X		
Assess all solicited AEs	Section 7.1.1 and 7.1.3					X		
Assess all unsolicited AEs	Sections 7.1.2 and 7.1.3	X	X	X	X	X		

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	Visit Type	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Phone Call**	**Clinic Visit**
	Study Day	**-21 to -3**	**1**	**4**	**8**	**15**	**22**	**29**
	Visit Window (Days)	**n/a**	**n/a**	**n/a**	**-1/+1**	**-1/+1**	**n/a**	**-2/+2**
	Visit Number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**
Study Event	**References**							
Assess SAEs	Section 7.1.4	X	X	X	X	X	X	X
Assess AESIs	Section 7.1.4.1	X	X	X	X	X	X	X
Assess NOCDs, medically attended AEs, AEs leading to withdrawal	Sections 7.1.3	X	X	X	X	X	X	X
Assess relevant medications	Sections 5.1.2 and 6.5	X	X	X	X	X	X	X
Blood draws for Immunogenicity and Exploratory Objectives								
Serum Blood Draw (Primary and Secondary Objectives; 10 mL)	Section 3.5.		X_a		X			X
Serum Blood Draw (Exploratory Objectives; 5 mL)	Section 3.5.		X_b	X	X			
Whole Blood Draws (Exploratory Objectives; 2 mL)	Section 3.5.		X_c	X				
Whole Blood Draw (Exploratory Objectives; 5 mL)	Section 3.5.		X_d	X	X			

Whole Blood Draw (Exploratory Objectives; 50 mL)	Section 3.5.		X_a		X			X

Notes:
a. Procedure must be performed prior to vaccination
b. Three Serum Blood Draws (3 x 5ml) must be taken at Study Day 1, i.e. at baseline (prior to vaccination), at 6h and at 24h after vaccination.
c. Six whole Blood Draws (6 x 2 mL) must be taken at Study Day 1, i.e. at baseline (prior to vaccination) and at 1, 2, 4, 8 and 24h after vaccination.
d. Three Whole Blood Draw (3 x 5 mL) must be taken at Study Day 1, i.e. at baseline (prior to vaccination), at 6h and at 24h after vaccination

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Table 4: Time and Events Table – Follow-up Period (until Day 366)

	Visit Type	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Phone Call**	**Phone Call**	**Clinic Visit**
	Study Day	**85**	**113**	**181**	**209**	**271**	**366**
	Visit Window (Days)	**-7 to +7**	**-7 to +7**	**-7 to +7**	**-14 to +14**	**-14 to +14**	**-14 to +14**
	Visit Number	**7**	**8**	**9**	**10**	**11**	**12**
Study Event	**References**						
Safety							
Assess SAEs	Section 7.1.4	X	X	X	X	X	X
Assess AESI	Section 7.1.4.1	X	X	X	X	X	X
Assess NOCDs, medically attended AEs, AEs leading to withdrawal	Sections 7.1.4.1 and 7.1.3	X	X	X	X	X	X
Assess relevant medications	Sections 5.1.2 and 6.5	X	X	X	X	X	X
Blood draws for Immunogenicity and Exploratory Objectives							
Serum Blood Draw (Secondary Objective; 10 mL)	Section 3.5			X			

Whole Blood Draw (Exploratory Objectives; 50 mL)	Section 3.5			X			
Study Completion Procedures							
Study Termination[a]	Section 5.5						X

Notes:
a. Subjects who terminate the study early are recommended to complete certain study-related procedures. See section 5.5 for further details.

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LIST OF ABBREVIATIONS

ADCC	Antibody-dependent cell mediated cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BZN	Benzonaphthyridines
CBER	Center for Biologics Evaluation and Research
cDNA	Complementary deoxyribonucleic acid
CI	Confidence interval
CRF	Case report form
CRM_{197}	Cross Reacting Material 197
CSR	Clinical Study Report
DMC	Data Monitoring Committee
EC	Ethics committee
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
ELISPOT	Enzyme-Linked ImmunoSpot
EMA	European Medicines Agency
FACS	Fluorescence-activated cell sorting
FAS	Full analysis set
FDA	Federal Drug Agency
GCP	Good clinical practice
GMC	Geometric mean concentration
GMP	Good manufacturing practice

GMT	Geometric mean titer
GMR	Geometric mean ratio
HEENT	Head, ears, eyes, nose and throat
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
hSBA	Human complement serum bactericidal assay
ICF	Informed consent form
ICH	International Committee for Harmonization
IM	Intramuscular
IRB	Institutional review board
IV	Intravenous
LLQ	Lower limit of quantification
MenC	Meningococcal type C
MPL	Monophosphoryl lipid A
NCR	No carbon required
NOCD	New Onset of Chronic Disease
PEG	Polyethylene glycol
PO	Per oral
PP	Per protocol
RNA	Ribonucleic acid (RNA
SAE	Serious Adverse Event
SMIP	Small molecule immune potentiator
TLR	Toll-like receptor
VSAE	Vaccine serious adverse event

1.0 BACKGROUND AND RATIONALE

1.1 Background

MenC-CRM$_{197}$ Conjugate Vaccine

Meningococcal disease worldwide is predominantly a disease of infants and young children. *N. meningitidis* serogroup B and C remain the most prevalent strains in North America and Europe, (Rosenstein, N. et al., 2001) and together cause more than 95% of reported cases of meningococcal disease in Europe (Connolly, M, et al., 1999). In Europe, *N. meningitidis* serogroup C (MenC) is one of the major serogroups causing invasive disease. Case fatality in Germany has ranged between 6% and 8% between 1999 and 2006, and has remained generally consistent across the different European countries, varying between 6-11%, with the case fatality rate being notably higher for serogroup C disease than for serogroup B (European Centre for Disease Prevention and Control, 2011). Since Men C vaccination was added to Germany's routine schedule for children in 2006, there has been a reported decline in Men C incidence. However, the decline was not as rapid when compared to other European countries (Hellenbrand, W. et al., 2013)

The Novartis Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) comprises MenC oligosaccharides conjugated to the protein carrier, CRM$_{197}$, a nontoxic mutant of diphtheria toxin. The vaccine has been shown to be safe and immunogenic and able to prime infants, toddlers and young children for immunological memory (see Novartis Meningococcal C-CRM$_{197}$ Conjugate Vaccine Investigator Brochure).

In Germany, the Standing Committee on Vaccination (STIKO) of the Robert Koch Institute recommends a single dose of MenC conjugate vaccine in children over the age of 12 months as part of the routine vaccination campaign (Robert Koch Institute Epidemiologisches Bulletin, August 2013). For specific indications, e.g. in case of postexposure prophylaxis, the recommended schedule for primary immunization of infants between 2 to 12 months of age with a MenC conjugate vaccine is two dosages given with an interval of at least 2 months.

Although the Novartis Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) represents an example of how vaccination with a well characterized, purified polysaccharide antigen can yield pivotal public health triumphs, there remains a need for further improvement of the MenC vaccine. A more potent MenC vaccine formulation might yield an increase in the magnitude of the antigen-specific immune response enabling a reduction of the antigen dosage. Furthermore, induction of a more rapid antigen-specific immune response may enable a reduction in the number of doses needed for post-exposure prophylaxis in infants.

Vaccine Adjuvants

Immunization with purified protein or polysaccharide antigens typically results in the induction of a modest antibody response with little or no T cell response when compared to vaccines comprised of whole or killed bacteria or viruses that have inherent

immunepotentiating activity. The need to increase the immunogenic response of wellcharacterized and purified antigens that display suboptimal immunogenicity when used alone affirms the essential role for the use of adjuvants. Vaccine adjuvants may significantly reduce the amount of antigen needed (Del Giudice, G, et al., 2013) and may induce a more rapid immune response enabling a reduction in the number of doses in a regimen.

Besides reducing the antigen dosage or number of doses in the vaccine regimen, there is now an increased appreciation of the capacity of adjuvants to increase not just overall antibody titer but also to increase the number of functional antibodies and/or antibodies with higher affinity for vaccine antigens. Many pathogens, such as influenza viruses, HIV, human papilloma virus (HPV) and the malaria parasite, display substantial antigenic drift, subtype and/or strain variations. Therefore, the ability of adjuvants to broaden an immune response profile could be crucial to the success of vaccines against such targets. Previous studies have shown that the broadening effect of adjuvants may be mediated via expansion of B cell diversity, not merely through increased titers (Khurana, et al., 2010, 2011). Clinically, antibody response broadening by adjuvants such as AS04 or oil-inwater emulsions has been demonstrated in HPV vaccines and influenza, respectively (Bissett, SL et al., 2014; Del Giudice, G et al., 2013).

One unmet need is the development of vaccines for effective T cell responses. Several vaccines in development are aimed at eliciting T cell responses, which historically have not been induced by the most commonly used adjuvants in vaccines for human use, such as aluminium hydroxide. Therefore, an objective of many adjuvant discovery and development programs is to elicit more effective engagement of T-helper cells for optimizing the quality, breadth and durability of antibody responses, or, to induce effector CD4+ or CD8+ T cells to kill intracellular pathogens. One approach for new generation vaccines is the use of agonists for Toll-like receptors (TLRs) that activate innate immune receptors, mainly on antigen presenting cells, and facilitate the generation of T helper cell responses.

Adjuvants that are currently employed in human vaccines licensed for use in the USA and/or Europe include aluminium salts, oil-in-water emulsions (MF59, AS03 and AF03), virosomes, and AS04 (Alving, CR, et al., 2012). Among the most advanced adjuvants systems is AS04 which is used in the Cervarix® HPV vaccine and consist of the TLR4 ligand monophosphoryl lipid A (MPL) combined with aluminium salt. MPL, along with QS21, is also part of the adjuvant system (AS01) in the RTS, S malaria vaccine from GlaxoSmithKline which has been evaluated in a Phase 3 clinical trial (Regules, JA, et al.,

2011). Another clinically advanced adjuvant is CpG oligodeoxynucleotide (ODN), a TLR9 ligand contained in the Heplisav® vaccine candidate for hepatitis B from Dynavax, that has completed a Phase 3 clinical trial (Reed, SG, et al., 2013).

Small molecule immune potentiators as a new class of vaccine adjuvants

A new class of adjuvants, small molecule immune potentiators (SMIPs), has been identified that activate immune cells by targeting TLR7 and TLR8. Imiquimod and Resiquimod (R848) are clinically advanced TLR7 and/or TLR8 SMIPs that are used as immunotherapeutics. Although Imiquimod and Resiquimod have been studied extensively as vaccine adjuvants in preclinical models (Vasilakos et al. 2013), they were never optimized for this use and, in general, compare poorly to other pre-clinical and clinical adjuvant candidates. Furthermore, when Imiquimod is applied topically (it is a licensed topical treatment for viral and malignant skin lesions) it induces strong local and systemic inflammatory reactions, and is poorly tolerated (Bauza, et al. 2009; Campanelli, et al. 2005; Meyer, et al. 2008).

Unlike traditional drugs, TLR7 SMIPs activate innate immunity and initiate a cascade of immune responses that can have systemic impact and endure after the compound has been cleared from the organism. For SMIPs as vaccine adjuvants this difference is highlighted further by the fact that 2-3 local IM injections drive antigen-specific B and T cell responses at distal sites and these can provide protection in the form of immunologic memory (Tacken, et al. 2011; Ilyinskii, et al., 2014). Therefore, limiting the systemic exposure of the SMIP adjuvants has been postulated as an approach to both increase vaccine efficacy and minimize side effects associated with systemic and generalized inflammation. Novartis is currently developing a novel adjuvant, containing a SMIP from the benzonaphthryridines (BZN) series, LHD153, which targets TLR7. The objective driving the discovery of this new TLR7 ligand was to develop a vaccine adjuvant with high efficacy in increasing the vaccine specific immune response and with minimal side effects. To obtain this objective it was postulated that the ideal compound would remain localized at the site of injection to help trigger the immune reaction to vaccine antigens, yet maintain a low systemic distribution. At the same time this compound had to be soluble to make industrial scale-up and manufacturing feasible. Soluble BZN were engineered so that they could be formulated with aluminium salts with the aim of limiting their systemic exposure and keeping them localized in the muscle for short time after immunization. The strongest adsorption to aluminium hydroxide particles is obtained through ligand exchange of hydroxyl and/or phosphate groups on the surface of aluminium hydroxide or phosphate with soft anionic moieties such as phosphates, phosphonates, phosphites, sulfates and carboxylates. To drive the adsorption to aluminium hydroxide through ligand exchange, LHD153 was functionalized with a polyethylene glycol (PEG) linker and a terminal phosphonate. Furthermore, LHD153 was

stabilized with arginine salt to allow scale up for GMP manufacturing, yielding LHD153R. As predicted, unformulated LHD153R exhibited high levels of systemic exposure when injected IM in mice, rats and dogs, whereas the serum concentrations of LHD153R adsorbed to aluminium hydroxide (aluminium hydroxide/LHD153R) was dramatically reduced. Moreover, aluminium hydroxide/LHD153R remained localized to the injection site.

Preclinical studies using aluminium hydroxide/LHD153R to date confirm the activation of the TLR7 pathway and subsequent boost of both the humoral and cellular immune response. Moreover, aluminium hydroxide/LHD153R displays a unique pharmacokinetic profile as demonstrated by its minimal systemic exposure, potentially minimizing any systemic inflammatory response associated with tolerability issues. Aluminium hydroxide/LHD153R has achieved proof of concept in animal models using several vaccine antigens including MenC, MenB, rabies, HIV and respiratory syncytial virus (RSV). In vitro toxicity of LDH153R has been assessed, and in vivo nonclinical tolerability and safety of LHD153R and aluminium hydroxide/LHD153R have been evaluated in rats, dogs and non-human primates. LHD153R was not phototoxic, genotoxic or mutagenic (Ames and chromosomal aberration tests), and did not cause local or systemic toxicity in dogs or rats. Furthermore, aluminium hydroxide/LHD153R was well tolerated in rhesus monkeys.

1.2 Rationale

The aim of this study is to assess the safety of aluminium hydroxide/LHD153R adjuvanted MenC-CRM$_{197}$ conjugate vaccine (MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R) and to compare the antibody-mediated immune response elicited by MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R with the licensed aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®).

Furthermore, a comprehensive set of exploratory objectives has been selected to assess the systemic exposure of LHD153 after intramuscular injection and to evaluate the quality of the specific immune response against MenC-CRM$_{197}$ in detail and to evaluate biomarkers that may be predictive of safety and/or innate immune activation.

The licensed Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) has been chosen as the primary vaccine candidate to assess the safety and immunopotentiating properties of aluminium hydroxide/LHD153R for several reasons. Firstly, the safety and immunogenicity profiles of the Meningococcal C-CRM$_{197}$ Conjugate Vaccine have been well established through years of commercial use. Secondly, a more potent Meningococcal C-CRM$_{197}$ Conjugate Vaccine might enable a reduction of the antigen dosage or the number of doses needed in infants between 2 and 12 months of age. Finally,

the Meningococcal C-CRM$_{197}$ conjugate is a well-characterized, single antigen preparation which provides an ideal setting to explore the potential of this new aluminium hydroxide/LHD153R adjuvant.

2.0 OBJECTIVES

2.1 Primary Objectives

Primary Safety Objective

To assess the safety of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R as compared to that of aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine.

Primary Immunogenicity Objective

To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine at Day 29, as measured by human complement serum bactericidal assay (hSBA) directed against *N meningitidis* serogroup C.

2.2 Secondary Objectives

Secondary Immunogenicity Objective(s)

1. To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal CCRM$_{197}$ Conjugate Vaccine at Day 8 and Day 181 after vaccination, as measured by hSBA directed against *N. meningitidis* serogroup C. Baseline antibody titers will also be measured by hSBA.
2. To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal CCRM$_{197}$ Conjugate Vaccine, at Day 8, Day 29 and Day 181 after vaccination, as measured by an enzyme-linked immunosorbent assay (ELISA) to *N. meningitidis* serogroup C. Baseline antibody concentrations will also be measured by ELISA.

2.3 Exploratory Objectives

1. To evaluate the systemic exposure of LHD153 at several early time-points after IM injection of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R or Meningococcal CCRM$_{197}$ Conjugate Vaccine.

2. To explore the frequency of B cells specific for Men C polysaccharide and CRM_{197} protein at baseline (Day 1) and at Day 8, Day 29 and Day 181 after vaccination with MenC-CRM_{197}/Aluminium Hydroxide/LHD153R or the aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine. Subsequently, the B cell repertoire of the antigen specific B cells and the specific antibody functionality will be analyzed in a selected subset of subjects.
3. To explore the baseline T cell mediated immunity to CRM_{197} and to evaluate the frequency and quality of CRM_{197} specific T cells induced by MenCCRM$_{197}$/Aluminium Hydroxide/ LHD153R compared to aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine at Day 8 and Day 29.
4. To evaluate biomarkers that may be predictive for safety and/ or innate immune activation.

3.0 STUDY DESIGN

3.1 Overview of Study Design

This is a Phase 1, randomized, observer blind, adjuvant dosage-escalation study. It will be performed at a single center. In total, approximately 80 healthy male and healthy nonpregnant female adults (18-45 years of age) will be enrolled in the study.

Subjects will be randomized to receive a single IM vaccination of either the licensed aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (Menjugate®) or the investigational vaccine, MenC-CRM_{197}/Aluminium Hydroxide/LHD153R.

The dosage of LHD153R will be escalated from 12.5 µg to 100 µg. For the dosageescalation of LHD153R, the subjects will be enrolled into 1 of 4 cohorts, in a stepwise manner with 20 subjects per cohort. Subjects in all cohorts will be randomized in a 1:4 ratio, to receive either aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (control) or MenC-CRM_{197}/Aluminium Hydroxide/LHD153R with increasing doses of LHD153R.Cohort 1 will receive 12.5 µg of LHD153R; Cohort 2 will receive 25 µg of LHD153R; Cohort 3 will receive 50 µg of LHD153R; and Cohort 4 will receive 100 µg of LHD153R (Table 3.1-1).

Table 3.1-1: Subjects Randomized per Cohort and Treatment Dose Group

Cohort	Group	Subjects/ Group	MenC Dosage* (µg)	Adjuvant Dosages		Total Volume/Dose	Total Subjects/Group
				Aluminium Hydroxide (mg)	LHD153R (µg)		
1	A	4	10	1	0	0.5 mL	20
	B	16	10	1	12.5	0.5 mL	
2	A	4	10	1	0	0.5 mL	20
	C	16	10	1	25	0.5 mL	
3	A	4	10	1	0	0.5 mL	20
	D	16	10	1	50	0.5 mL	
4	A	4	10	1	0	0.5 mL	20
	E	16	10	1	100	0.5 mL	

*Conjugated to 12.5-25 µg CRM_{197}

All cohorts will have a staggered entry. For each cohort, the first 5 subjects (i.e. the first 1:4 randomization block) to receive either aluminium hydroxide adjuvanted

Meningococcal C-CRM$_{197}$ Conjugate Vaccine (n=1) or MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R (n=4) will be vaccinated at rate of 1 subject each day.

After entry of the first 5 subjects in each cohort, the enrollment will be paused. The remaining 15 subjects for each cohort will be enrolled only after DMC review of the safety results obtained through Day 15 has been finalized (Table 3.1-2). Furthermore, after entry of all 20 subjects in each cohort, enrollment will be paused again. Enrollment of the first 5 subjects in the next cohort will only proceed after the Day 29 safety results of the previous cohort have been reviewed by the DMC.

Table 3.1-2: Overview of staggered entry of subjects for each cohort

Cohort	1st Stage of enrollment	MenC-CRM$_{197}$/ Aluminium Hydroxide	MenC-CRM$_{197}$/ Aluminium Hydroxide /LHD153R	2nd Stage of enrollment	MenC-CRM$_{197}$/ Aluminium Hydroxide	MenC-CRM$_{197}$/ Aluminium Hydroxide /LHD153R
1	First 5 subjects with vaccination rate of 1 subject/day	1	4	Remaining 15 subjects, after DMC review of Day 15 safety results	3	12
2		1	4		3	12
3		1	4		3	12
4		1	4		3	12

Post-vaccination procedures include collection of urine specimens at Day 8 and Day 29 for safety analysis and blood specimens at Day 8, Day 29 and Day 181 for safety assessment and evaluation of the primary and secondary immunogenicity endpoints. Furthermore, additional blood specimens will be collected for assessment of exploratory endpoints at Day 1, Day 4, Day 8, Day 29 and Day 181 from those subjects that signed an additional informed consent concerning blood collection for exploratory assessment.

3.2 Study Period

Each subject should expect to participate in the study for approximately 12 months, from the time of enrolment through the last study visit.

3.3 Blinding Procedures

This study is designed as an observer-blind study. For each dosage cohort, subjects, investigators, laboratories and the sponsor will be blinded to vaccine assignments.

To maintain the blindness within each cohort, designated nurse(s) or physician(s) will be responsible for administering the study vaccines to the subjects, and will be instructed not to reveal the identity of the study vaccines neither to the subject nor to the investigative

site personnel (investigator, study nurse, monitor) involved in the conduct or monitoring of the trial. This (these) designated individual(s) will have no contact with the subjects after the administration of the study vaccine. Furthermore, unblinded monitors are assigned to reconcile actual vaccine treatment.

Study unblinding, at the group level, is planned for an Interim Analysis of the safety and immunogenicity data obtained up to Day 29 after all cohorts are enrolled and for full unblinding at the End of Study.

Except in the case of medical necessity, a subject's treatment should not be unblinded without the approval of the Sponsor. In such instance of medical emergency, every effort should be made to contact the Sponsor prior to unblinding. If unblinding should occur (by either accidental unblinding or emergency unblinding for a serious adverse event) prior to completion of the study, the investigator must promptly contact the Sponsor and document the circumstances on the appropriate forms. Instructions regarding emergency unblinding will be provided to the investigator.

3.4 Data Collection

3.4.1 Data Collected from Subjects

The following data will be collected from each subject over the duration of their study participation:

- Demographic Information
- Adverse Events
- Medical History
- Concomitant Medications

All data collected must only be identified using the Subject ID, as described in section 5.2.3.

3.4.2 Tools Used for Data Collection

Data will be recorded in the Subject Diary and collected on Case Report Forms (CRFs).

Subject Diary

Subject Diaries will be the only source document allowed for solicited local and systemic adverse events (including body temperature measurements), starting after the initial 24

hours post-vaccination observation period at the clinic. The following additional rules apply to documentation of safety information collected in the Subject Diary:

1. No corrections or additions to the Subject Diary will be allowed after it is delivered to the site.
2. Any blank or illegible fields on the Subject Diary must be described as missing in the CRF.
3. Any corrections to the Subject Diary must be performed by the person completing the Subject Diary and should include a single strike through line through the incorrect value or text with a brief explanation for each change, the initials of that person, and date of correction.

Case Report Forms

This study utilizes Case Report Forms (CRFs) to collect study-related data from each subject. A qualified site staff member(s) is required to enter subject data in the CRFs in English based on the medical information available in each subject's source record. The following additional rules apply to documentation of Subject Diary information collected in the CRFs:

1. The site must enter all readable entries in the Subject Diary into the CRF, including those values that may be biologically implausible (e.g. body temperature: 400°C).
2. Any illegible or implausible data should be reviewed with the subject. If an underlying solicited or unsolicited adverse event is described on review with the subject, this should be described in the source document and reported as an unsolicited adverse event in the Adverse Event CRF (e.g., if the subject above confirms body temperature of 40°C on the day in which body temperature: 400°C was written into his/her Subject Diary, this fever of 40°C should be recorded in the Adverse Event CRF).
3. Any newly described safety information (including a solicited adverse event) must not be written into the Subject Diary and must be described in the study file as a verbally reported adverse event. Any adverse event reported in this fashion must be described as an unsolicited adverse event and therefore entered on the Adverse Event CRF.

Data should be entered into the CRF in a timely fashion following each subject's clinic visit, study procedure, or phone call. Each subject's CRF casebook will be compared with the subject's source records by a Novartis-approved study monitor (or designee) over the duration of the study in order to ensure data collection accuracy.

3.5 Collection of Clinical Specimens

The following clinical specimens are required to be collected from each subject in this study:

- Blood
- Urine

Processing of each specimen should be completed by a qualified site member. Testing of clinical specimens will be performed by a Novartis or designated laboratory.

Blood Specimens

Before Vaccination

- At the Pre-vaccination Screening Visit (between Day -21 to -3) one sample of approximately 10 ml blood will be drawn from all subjects.
- At Visit 1 (Day 1) - prior to vaccination – two samples of approximately 10 ml blood will be drawn from all subjects.
- At Visit 1 (Day 1) - prior to vaccination - the following blood samples will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays:
  - One sample of approximately 2 ml
  - Two samples of approximately 5 ml
  - One sample of approximately 50 ml

After Vaccination

- At Visit 1 (Day 1) - 1 hour after vaccination - one sample of approximately 2 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 2 hours after vaccination - one sample of approximately 2 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 4 hours after vaccination - one sample of approximately 2 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.

- At Visit 1 (Day 1) - 6 hours after vaccination – two samples of approximately 5 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 8 hours after vaccination - one sample of approximately 2 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 24 hours after vaccination - the following blood samples will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays:
  - One sample of approximately 2 ml
  - Two samples of approximately 5 ml
- At Visit 2 (Day 4) the following blood samples will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays:
  - One sample of approximately 2 ml
  - Two samples of approximately 5 ml
- At Visit 3 (Day 8) two samples of approximately 10 ml blood will be drawn from all subjects.
- At Visit 3 (Day 8) the following blood samples will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays
  - Two samples of approximately 5 ml
  - One sample of approximately 50 ml
- At Visit 6 (Day 29) two samples of approximately 10 ml blood will be drawn from all subjects.
- At Visit 6 (Day 29) one sample of approximately 50 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 9 (Day 181) one sample of approximately 10 ml blood will be drawn from all subjects.
- At Visit 9 (Day 181) one sample of approximately 50 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.

The blood will be used for screening and safety laboratory assessments, immunological serology assays, pharmacokinetic analysis, cell mediated immunity assays and gene expression and protein production assays. See section 5.1.2, section 5.2.1 and section 7.0 for additional details.

Processing of each blood specimen should be completed in accordance with the study specific Clinical Specimen Laboratory Manual.

The total amount of blood collected over the study period for all subjects will be approximately 80 ml.

For subjects that signed an additional informed consent for blood collection for exploratory assays the total amount of blood collected over the study period will be approximately 344 ml.

Urine Specimens

Urine will be collected at the Pre-vaccination Screening Visit (between Day -21- to -3), at Visit 1 (Day 1; before vaccination), at Visit 3 (Day 8) and at Visit 6 (Day 29). Results will be recorded in the source document and CRF.

Urine will be collected from all subjects for safety laboratory assessments and drugs-ofabuse testing. Furthermore, urine will be collected for pregnancy testing in all females.

3.6 Stopping/Pausing Guidelines

Stopping/pausing guidelines are predefined criteria that halt the conduct of a study (either a vaccine group or the entire study). These guidelines are used to ensure the safety of study subjects.

The following criteria, with grading scales (see Appendix A to E), adapted from the CBER Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive vaccine Clinical Trials", will be used for this study:

Enrollment into the study will be paused for an unscheduled safety analysis if any of the following events occur across any subject groups:

- One or more vaccine-related Grade 4 AE
- Six or more of the following, in any combination:
  - Vaccine-related Grade 3 AEs.

- Vaccine-related Grade 3 AEs leading to study withdrawal.

After thorough analysis of the events (and possible unblinding), the DMC will decide if dosing should resume (see section 3.7).

3.7 Data Monitoring Committee

A DMC will be formed to review safety data during scheduled periodic reviews. The DMC may also perform reviews on an ad hoc basis. DMC membership will consist of 3 individuals who are external to the site and sponsor, and will include 1 statistician who is independent from the study team.

Subjects will be enrolled in a stepwise manner in each of the four vaccine dosage cohorts (Cohort 1: 12.5 µg LHD153R, Cohort 2: 25 µg of LHD153R, Cohort 3: 50 µg of LHD153R and Cohort 4: 100 µg of LHD153R). The DMC will review all safety data, as described in the DMC charter and in the statistical analysis plan, after the first 5 subjects in each cohort have completed Visit 4 (Day 15) and their data are available for analysis, and before enrollment of the remaining subjects in each cohort. In addition, the DMC will review all safety data after enrollment in each cohort has been completed, after Visit 6 (Day 29) data are available for analysis/review and before proceeding with enrollment of the subsequent cohort.

The specific roles and responsibilities of the DMC members and other personnel involved will be documented in the DMC charter. The DMC charter will be finalized before the start of the study and will outline in detail all pausing and stopping rules according to the Clinical Study Protocol.

3.8 Premature Withdrawal from Study

Subjects may withdraw at any time, or be dropped from the study at the discretion of the investigator should any untoward effects occur and/or for safety reasons. In addition, a subject may be withdrawn by the investigator or the Sponsor if he/she violates the study plan or for administrative reasons. The investigator or study coordinator must notify the Sponsor immediately when a subject has been withdrawn due to an adverse event.

The circumstances above are referred to as premature withdrawal from the study, and the reason for premature withdrawal should be clearly documented and detailed in the source documentation. The investigator should make every attempt to evaluate the subject's safety, including resolution of ongoing AEs, at the time of premature withdrawal. If a subject wants to withdraw from the study prior to the last planned study visit, the subject will be asked to be followed for safety for the duration of the study. When a subject

withdraws, or is withdrawn, from the study, the procedures described in section 5.5.1 should be completed if possible.

The reasons for premature withdrawal from the study include: Adverse event, death, withdrawal of consent, lost to follow-up, administrative reason, and protocol deviation. These reasons are described in greater detail below.

Adverse Event

For any subject withdrawn from study participation prior to the planned Study Termination Visit, it is important to determine if an AE was associated with the reason for discontinuing the study. This AE must be identified on the AE CRF page by indicating "Withdrawn from study due to AE". Any ongoing AEs at the time of study withdrawal must be followed until resolution or stabilization.

Death

For any subject withdrawn from study participation due to death, this should be noted on the Study Termination CRF page and the associated SAE that led to the death must be reported.

Withdrawal of consent

The subject can withdraw consent for participation in the study at any time without penalty or loss of benefit to which the subject is otherwise entitled. Reason for early termination should be deemed as "withdrawal of consent" if the subject withdraws from participation due to a non-medical reason (i.e., reason other than AE). If the subject intends to withdraw consent from the study, the investigator should clarify if the subject will withdraw completely from the study or if the subject will continue study participation for safety, or a subset of other study procedures. If the subject requests complete withdrawal from the study, no further study interventions will be performed with the subject.

Lost to Follow-Up

For subjects who fail to show up for study visits (clinic or telephone contacts), study staff is encouraged to make at least three documented attempts to contact the subject by telephone and at least one documented written attempt to contact the subject to encourage the completion of study termination procedures. These efforts to contact the subject must be recorded in the source document. The termination date for the subject to be captured

on the Study Termination CRF page is the date of the last contact (clinic visit or telephone) with the subject.

Administrative Reason

Examples for subjects withdrawn from the study due to administrative reason can include: Sponsor decision to terminate the study, subject meeting a pre-specified withdrawal criterion, subject discontinuation for insurance issues, moving, no time, etc. This reason should be noted in the Study Termination CRF page and any ongoing AEs at the time of study withdrawal must be followed until resolution/stabilization.

If the clinical study is prematurely terminated by the Sponsor, the investigator is to promptly inform the study subjects and local EC/IRB and should assure appropriate therapy and follow up for the subjects. All procedures and requirements pertaining to the archiving of study documents should be followed. All other study materials (study medication/vaccines, etc.) must be returned to the Sponsor.

For subjects who are withdrawn from the study due to receipt of an excluded medication/vaccination or due to significant protocol non-compliance, this reason should be noted in the Study Termination CRF page.

Protocol Deviation

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. In general, subjects associated with protocol deviations may remain in the study unless continuation in the study jeopardizes the subject's health, safety, or rights.

Investigators will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a change to the protocol would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/EC and health authorities it cannot be implemented.

Any subject who becomes pregnant during the study should be encouraged to continue participating in the study for safety follow-up. The site must complete a Pregnancy Report CRF (initial report) as soon as possible after learning of pregnancy occurrence (see section 7.1.6 for further details). If the subject withdraws from the study for any of the above categories except death, the site will obtain permission from the subject to

continue to remain in contact with her until the outcome of the pregnancy is known, even if the outcome is not known until after the subject reaches the end of the routine study period.

3.9 End of Study

Most clinical trials intended to support the efficacy/immunogenicity and safety of an Investigational Product proceed to full completion of planned sample size accrual.

A subject is considered to have completed this study when he/she has: (1) received the intended dose of study vaccine and (2) completed 365 days (Visit 12) of safety follow-up after receiving the study vaccine.

Evaluation of the primary and/or secondary immunogenicity objectives requires the testing of biological samples from all study subjects, which can only be completed after all samples are collected. The last samples for the analysis of the primary and/or secondary objectives will be taken at Visit 9 (Day 181). For the purpose of this protocol, End of Study is defined as the completion of the testing of such biological samples, to be achieved no later than 8 months after collection of the last biological sample at Visit 9.

4.0 SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

In order to participate in this study, all subjects must meet all of the inclusion criteria described.

1. Male or female individuals of 18 through 45 years of age on the day of informed consent.
2. Healthy volunteers with good physical and mental health status, determined on the basis of the medical history, a physical examination and the results of the screening tests as judged by the investigator.
3. Individuals who have voluntarily given written informed consent after the nature of the study has been explained according to local regulatory requirements, prior to study entry.
4. Individuals who can comply with study procedures including follow-up[1].
5. Individuals that are able to understand, read and write German language.
6. Females of childbearing potential who are using an effective birth control method[2] which they intend to use for at least 30 days after the study vaccination.

4.2 Exclusion Criteria

Each subject must not have or must not be:

1. Progressive, unstable or uncontrolled clinical conditions.
2. Hypersensitivity, including allergy, to any component of vaccines, medicinal products or medical equipment whose use is foreseen in this study.

[1] A subject is considered to be compliant if the Investigator judges that the subject will complete the Subject Diary, return for all the follow-up visits and be available for telephone calls as scheduled in the study.

[2] The following birth control methods are considered effective:

- Abstinence
- Hormonal contraceptive (such as oral, injection, transdermal patch, implant) if used for at least 30 days prior to informed consent
- Diaphragm with spermicide, tubal occlusion device
- Intrauterine device (IUD)

- Tubal ligation
- Male partner using condom with spermicide
- Male partner having been vasectomized at least six months prior to informed consent

3. Clinical conditions representing a contraindication to intramuscular vaccination and blood draws.
4. Abnormal function of the immune system resulting from:
   a. Clinical conditions.
   b. Systemic administration of corticosteroids (PO/IV/IM) for more than 14 consecutive days within 90 days prior to informed consent.
   c. Administration of antineoplastic and prescription immunomodulating agents or radiotherapy within 90 days prior to informed consent.
5. Received immunoglobulins or any blood products within 180 days prior to informed consent.
6. Received an investigational or non-registered medicinal product within 30 days prior to informed consent or intend to participate in another clinical study at any time during the conduct of this study.
7. Vulnerable subjects (e.g. persons kept in detention), study personnel or an immediate family or household member of study personnel, subjects with legal incapacity or limited legal capacity
8. Any relevant deviation from the laboratory parameters at screening as judged by the investigator.
9. Previously received any vaccine that included a meningococcal C antigen.
10. Previously suspected or confirmed disease caused by *N. meningitides.*
11. Had household contact with and/or intimate exposure to an individual with culture proven *N. meningitides* serogroup C.
12. A positive serum or urine pregnancy test prior to the study vaccine administration or are currently lactating.
13. A positive drugs-of-abuse test prior to the study vaccine administration
14. Received any other vaccines within 30 days prior to enrolment in this study or who are planning to receive any vaccine within 30 days from the administration of study vaccines.

15. Any other condition that, in the opinion of the investigator, might interfere with the results of the study or pose additional risk to the subject due to participation in the study.

4.3 Criteria for Delay of Vaccination or Blood Draw

There may be instances when individuals meet all eligibility criteria for vaccination or blood draw yet have a transient clinical circumstance which may warrant delay of vaccination or blood draw. Under such circumstances, a subject may be considered eligible for study enrolment after the appropriate window for delay has passed and inclusion/exclusion criteria have been rechecked, and if the subject is confirmed to be eligible.

Reasons for delay of vaccination include:

- Body temperature elevation ≥38.0°C (measured orally) within 3 days prior to intended study vaccination.
- Use of antipyretics and/or analgesic medications within 24 hours prior to vaccination.

Reasons for delay of blood draw include:

- Subject has received a dose of systemic antibiotics less than 6 days before blood collection for the hSBA directed against *N meningitidis* serogroup C.

5.0 STUDY PROCEDURES

The sections that follow provide an overview of the procedures that are to be followed in enrolling, evaluating, and following subjects who participate in this clinical study. Visits can be either clinic visits or safety follow-up telephone calls, as specified in the Table below and in the Time and Events Tables 3 and 4 of the Study Synopsis.

Table 5.0-1: Study procedures

Visit Category	Procedures
Pre-vaccination Clinic Visit	Section 5.1 describes procedures to be followed prior to subject enrollment, including: informed consent and screening procedures.
Vaccination Clinic Visit	Section 5.2 describes procedures to be followed during the vaccination clinic visit, including: prevaccination procedures, enrolment, randomization, vaccination and post-vaccination procedures.
Post-vaccination Visits	Section 5.3 describes follow-up clinic visits and safety follow-up calls.
Unscheduled Visits	Section 5.4 describes possible procedures to be followed at unscheduled clinic visit.
Study Termination Visit	Section 5.5 describes procedures to be followed at the last study visit for a subject (may include early termination visit).

5.1 Pre-vaccination Clinic Visit(s)

The Pre-vaccination Clinic Visit must be performed in the period between Day -21 and Day -3.

This section describes the procedures that must be performed for each potential subject prior to enrollment, including obtaining informed consent and screening.

5.1.1 Informed Consent

"Informed consent" is the voluntary agreement of an individual or his/her legal guardian(s) to participate in research. Consent must be given with free will of choice, and without undue inducement. The individual must have sufficient knowledge and understanding of the nature of the proposed research, the anticipated risks and potential benefits, and the requirements of the research to be able to make an informed decision.

Informed consent following local IRB/EC guidance **must** be obtained before conducting any study-specific procedure (i.e., all of the procedures described in the protocol). Prior to any additional blood sample collection for exploratory objectives, a secondary informed consent **must** be signed by subjects. The process of obtaining informed consent should be documented in the subject source document in addition to maintaining a copy of the signed and dated informed consent.

5.1.2 Screening

After an individual has consented to participate in the study and informed consent is signed, that individual will be given a unique Screening Number. The subject's unique Screening Number will be documented in the Screening and Enrolment log. The eligibility of the subject will be determined based on the inclusion and exclusion criteria listed in section 4.0 and evaluated during this screening procedure.

Screening procedures at the Pre-vaccination Clinical Visit (between Day -21 and Day -3) will include the following:

- Review of demographic data, including age, gender, race, body weight and height.
- Review of medical history, including but not limited to any medical history, ongoing illnesses or injuries that may be relevant to subject eligibility for study participation. Relevant medical history can also include any medical history that contributes to the understanding of an adverse event that occurs during study participation, if it represents an exacerbation of an underlying disease/pre-existing problem.
- Perform physical examination, including but not limited to:
  - Assessment of general appearance
  - Collection of vital signs, including body temperature, blood pressure and respiratory rate
  - Examination of head, ears, eyes, nose and throat (HEENT)
  - Examination of skin
  - Auscultation of heart and lungs
- Collection and review of prior and concomitant medications or vaccinations taken prior to start of study (refer to section 6.5 for further details).
- Collection of any unsolicited AEs occurring prior to administration of the study vaccine.

- Blood draw (approximately 10 ml) for Safety Laboratory assessments, measurement of Hepatitis B surface antigen, anti-Hepatitis C virus antibodies, anti-HIV 1 and 2 antibodies and serum pregnancy test (all women).
- Urine sample for Safety Laboratory assessments and drugs-of-abuse testing.

NOTE: A general physical examination is to be performed by a qualified health care practitioner. "Qualified health care practitioner" refers to any licensed health care professional who is permitted by institutional policy to perform physical examinations and who is identified within the Study Staff Signature Log

Data collected during the Pre-vaccination Screening Clinic Visit must be written in the source document (see section 9.1) and will be captured in the Screening CRF Forms .In the event that the individual is determined ineligible for study participation, he/she is considered a screen failure. The reason for screen failure must be documented in the Screening and Enrolment log.

5.2 Vaccination Clinic Visit(s)

This section describes the procedures to be performed at the Vaccination Clinic Visit (Visit 1, Day 1), including: pre-vaccination procedures, enrolment, randomization, prevaccination blood draw, vaccination and post-vaccination procedures.

5.2.1 Pre-vaccination Procedures

During pre-vaccination procedures at Visit 1 (Day 1), the eligibility of the subject will be confirmed based on the inclusion and exclusion criteria listed in section 4.0.

Pre-vaccination procedures at Visit 1 (Day 1) will include the following:

- Review of systems by means of a structured interview that queries the subject as to any complaints the subject has experienced across each organ system.
- Perform physical examination, including but not limited to:
  - Assessment of general appearance
  - Assessment of body weight and collection of vital signs, including body temperature, blood pressure and respiratory rate
  - Examination of head, ears, eyes, nose and throat (HEENT)
  - Examination of skin

- Auscultation of heart and lungs

- Urine sample for Safety Laboratory assessments, pregnancy testing (all women) and drugs-of-abuse testing.
- Collection of any unsolicited AEs occurring prior to administration of the study vaccine.
- Collection and review of prior and concomitant medications or vaccinations taken, or recalled, since the last visit (refer to section 6.5 for further details).
- One blood sample (approximately 10 ml) will be drawn from all subjects for serology testing.
- One blood sample (approximately 10 ml) will be drawn from all subjects for baseline safety laboratory assessment.
- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and volume of blood draws are provided in section 3.5.

NOTE: A general physical examination is to be performed by a qualified health care practitioner. “Qualified health care practitioner” refers to any licensed health care professional who is permitted by institutional policy to perform physical examinations and who is identified within the Study Staff Signature Log.

Data collected during pre-vaccination procedures at Visit 1 must be written in the source document (see section 9.1). In the event that the individual is determined ineligible for study participation, he/she is considered a screen failure. The reason for screen failure must be documented in the Screening and Enrolment log. If the individual is determined to be eligible for the study, he/she can be enrolled into the study.

5.2.2 Enrolment

After an individual is determined to be eligible for study participation, the investigator will enroll the subject into the Electronic Data Capture (EDC) system where the randomization to the treatment group will occur. The Screening Number ceases to be used and remains in the Screening and Enrolment Log only.

If for any reason, after signing the informed consent form (ICF), the subject who is eligible and enrolled fails to be randomized, this is called a randomization failure. In this case the early termination study procedures must be applied. The reason for all randomization failures should be recorded in the Screening and Enrolment Log and in the

source document as specified in the Source Data Agreement. The information on subjects who are randomization failures should be kept distinct from subjects who are screen failures, as described in section 5.1.2 and section 5.2.1

5.2.3 Randomization

Enrolled subjects will be randomized and automatically assigned a unique Subject ID. The Subject ID will be the subject's unique identification number for all CRFs and associated study documentation that will be used for the duration of the study.

If for any reason, after signing the informed consent form (ICF), the eligible subject is enrolled and randomized but fails to undergo treatment, this is an Early Termination and the reason should be recorded in source document as specified in the Source Data Agreement. The information on these Early Termination subjects should be kept distinct in the source documentation from randomization failures, which are described in section 5.2.2.

5.2.4 Vaccination

After completing the pre-vaccination procedures at Visit 1 (Day 1), administer the vaccine to the subject according to the procedures described in section 6.3. Observe the blinding procedures described in section 3.3.

5.2.5 Post-vaccination Procedures

The following post-vaccination procedures will be performed at Visit 1 (Day 1):

- After vaccination, the subject will be observed for at least 30 minutes for any immediate solicited adverse events, body temperature measurement and unsolicited adverse events. All safety data collected during this time are to be recorded in the subject's source document.
- After vaccination, the subject will be observed for at least 24 hours at the clinic including observation for solicited AEs, body temperature measurement and unsolicited AEs. All safety data collected during this time are to be recorded in the subject's source document.
- From those subjects that signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn in the first 24 hours after vaccination. Details regarding the number and volume of post-vaccination blood draws are provided in section 3.5.

After the initial 24 hours inpatient observation period, a Subject Diary will be used in this study to document solicited and unsolicited AEs until Day 15. The Subject Diary is the only source for collection of solicited AEs after the initial 24 hours inpatient observation period. Therefore, it is critical that the subject completes the Subject Diary correctly.

The following training regarding completion of the Subject Diary must be provided:

- The subject should be trained on how and when to complete each field of the Subject Diary.
- The subject should be trained on how to self-measure local solicited adverse events and body temperature. The measurement of solicited local adverse events is to be performed using the ruler provided by the site.
- The subject should be instructed how to perform body temperature measurement using the thermometer provided by the site. If the subject feels unusually hot or cold during the day, the subject should check body temperature. If the subject has fever, the highest body temperature observed that day should be recorded in the Subject Diary.

Subject Diary training should be directed at the individual(s) who will perform the measurements of adverse events and who will enter the information into the Subject Diary. This individual may not be the subject, but if a person other than the subject enters information into the Subject Diary, this person's identity must be documented in the Third Party Delegation section of the Subject Diary. Any individual that writes in the Subject Diary must receive training on completion of the Diary Card at the time of the visit. This training must be documented in the subject's source record.

The site should schedule the next study activity (clinic visit) with the subject.

The subject will receive a written reminder of the next planned study activity. The subject will be reminded to complete the Subject Diary and to contact the site if there are any questions, and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

5.3 Post-vaccination Visit(s)

5.3.1 Subject Diary Reminder, Safety Follow-up and/or Post-vaccination

Blood Draw Clinic Visits

Subject Diary reminder, Safety follow-up and/or post-vaccination blood draw clinic visits will be performed on Day 4 (Visit 2), Day 8 (Visit 3), Day 15 (Visit 4), Day 29 (Visit 6), Day 85 (Visit 7), Day 113 (Visit 8) and Day 181 (Visit 9)

At Day 4 (Visit 2) the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. All unsolicited AEs, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. Any concomitant medications or vaccinations associated with those events must also be recorded on the source documents.
- All subjects will be reminded to complete the Subject Diary and to contact the site if there are any questions, and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.
- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and volume of blood draws are provided in section 3.5.
- The site should schedule the next study activity (clinic visit) with the subject and the subject will receive a written reminder of the next planned study activity.

At Day 8 (Visit 3) the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. All unsolicited AEs, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. Any concomitant medications or vaccinations associated with those events must also be recorded on the source documents.
- The subject will be reminded to complete the Subject Diary and to contact the site if there are any questions, and to contact the site immediately (or as soon as the subject

is medically stable) if the subject has a medical condition that leads to hospitalization or an emergency room visit. The site should schedule the next study activity (clinic visit) with the subject and the subject will receive a written reminder of the next planned study activity.

- Blood draw (approximately 10 ml) from all subjects for Safety Laboratory assessments.
- Urine sample from all subjects for Safety Laboratory assessments.
- Blood draw (approximately 10 ml) from all subjects for serology testing.
- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and volume of blood draws are provided in section 3.5.

At Day 15 (Visit 4) the following procedures will be performed:

- The Subject Diary will be collected and reviewed. No changes to the Subject Diary should be done at the clinic visit. For details on the Subject Diary see sections 3.4.2, and 5.2.5. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. All unsolicited AEs until Day 15, solicited local and systemic AEs continuing beyond Day 15, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. All concomitant medications or vaccinations associated with those events must also be recorded on the source documents.
- The site should schedule the next study activity (safety phone call) with the subject.
- The subject will receive a written reminder of the next planned study activity. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

At Day 29 (Visit 6) the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. Any solicited local and systemic AEs continuing beyond Day 15, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. All concomitant

medications or vaccinations associated with those events must also be recorded on the source documents.

- Blood draw (approximately 10 ml) from all subjects for Safety Laboratory assessments.
- Urine sample from all subjects for Safety Laboratory assessments.
- Blood draw (approximately 10 ml) from all subjects for serology testing.
- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and volume of post-vaccination blood draws are provided in section 3.5.
- The site should schedule the next study activity (clinic visit) with the subject.
- The subject will receive a written reminder of the next planned study activity. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

At Day 85 and Day 113 (Visit 7 and Visit 8), the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. Any solicited local and systemic AEs continuing beyond Day 15, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. All concomitant medications or vaccinations associated with those events must also be recorded on the source documents.
- The site should schedule the next study activity (clinic visit) with the subject.
- The subject will receive a written reminder of the next planned study activity. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

At Day 181 (Visit 9), the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since

the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. Any solicited local and systemic AEs continuing beyond Day 15, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. All concomitant medications or vaccinations associated with those events must also be recorded on the source documents.

- Blood draw (approximately 10 ml) from all subjects for serology testing.
- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and volume of post-vaccination blood draws are provided in section 3.5.
- The site should schedule the next study activity (safety phone call) with the subject.
- The subject will receive a written reminder of the next planned study activity. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

5.3.2 Safety Follow-up Calls

Safety follow-up calls will be performed on Day 22 (Visit 5), Day 209 (Visit 10) and Day 271 (Visit 11) and include the following procedures:

- Safety follow-up calls are calls made to the subject by a healthcare professional designated on the site log. These calls will follow a script which will facilitate the collection of relevant safety information. The subject will be interviewed according to the script, and information relating to solicited local and systemic AEs persisting beyond Day 15 and unsolicited adverse events including SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal, and/or NOCD and concomitant medications or vaccinations associated with those events. All safety information described by the subject must be written down in a designated location within the source document and not written on the script used for the telephone call.
- The site should schedule the next study activity (clinic visit or study termination visit) with the subject.
- The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

5.4 Unscheduled Visits

An unscheduled visit describes a non-routine study visit triggered by a specific event. These could include anticipated or unanticipated adverse events or interventions.

The following procedures should be carried out for all unscheduled visits:

1. Evaluate the subject's vital signs body temperature, heart rate, and blood pressure and perform a symptom-directed physical examination.
2. Record any observed AEs in the source documents.
3. Record any concomitant medications or vaccinations associated with AEs in the source documents.

5.5 Study Termination Visit

The study termination visit is scheduled on Day 366 (Visit 12). The termination visit is a clinic visit. The date of termination is the date of the last contact in which the subject's health status was assessed or, in cases where the subject does not agree to any further safety follow-up, it is the date consent is withdrawn. This date should be recorded on the termination CRF page. For visit procedures to be performed for a subject whose planned study participation ends prematurely, please see section 5.5.1.

At the Study Termination clinic visit the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit.
- The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present.
- Medically attended AEs, SAEs, NOCDs, or AESIs will be recorded on source documents.
- All medications taken or vaccines received will also be recorded on the source documents.
- The site will review with the subject the plan of when information relating to the subject's participation in the study may be available (e.g., study results, treatment assignments). It will also be discussed how information relating to the subject's

participation in the study will be shared with the subject's healthcare provider, if the subject chooses to share this information.

- The site will complete the termination CRF page and this will mark the completion of the subject's participation in the study.

5.5.1 Early Termination Visit

When a subject is withdrawn from treatment or withdraws from the study, the investigator will notify the Sponsor and, when possible, will perform the procedures listed below.

The reason(s) for the early termination must be included in the subject's source documentation. If the Early Termination Visit is a telephone call, collect as much information as possible. Early Termination Visits include subjects who were randomized but not treated.

At the clinic visit or during the telephone call, the following procedures should be performed, when possible:

- Collection and review of Subject Diary (if not already collected).
- Interview of subject to collect unsolicited adverse events, medically attended AEs, AEs leading to withdrawal, SAEs, AESIs, and NOCD.
- Interview of subject to collect concomitant medications and/or vaccinations.
- Symptom-directed physical assessment, at least including measurement of vital signs (body temperature [via oral route], respiratory rate, blood pressure, heart rate) and a check of general appearance (in case of clinic early termination visit).
- Draw a blood sample (approximately 10 ml) and an urine sample for Safety Laboratory assessment (in case of clinic early termination visit).
- The site will review with the subject the plan of when information relating to the subject's participation in the study may be available (e.g., study results, treatment assignments). It will also be discussed how information relating to the subject's participation in the study will be shared with the subject's healthcare provider, if the subject chooses to share this information.
- The site will complete the termination CRF page and this will mark the completion of the subject's participation in the study.

6.0 TREATMENT OF SUBJECTS

All vaccines associated with this study are to be stored separately from other vaccines and medications in a secure location under appropriate storage conditions with temperature monitoring. **All vaccines associated with this study must be checked for expiration date prior to use. Expired vaccines must not be administered to subjects.**

6.1 Study Vaccine(s)

The term 'study vaccine' refers to those vaccines provided by the Sponsor, which will be evaluated as part of the study objectives. The study vaccines specific to this study are described in Table 6.1-1.

Table 6.1-1: Study Vaccine Composition

Group A (Control) Meningococcal C-CRM$_{197}$ Conjugate Vaccine	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM$_{197}$ protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
Sodium Chloride	3.5 mg
Sterile water for injection, up to	0.5 ml

Group B (12.5µg LHD153R) - MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	

Meningococcal C oligosaccharide conjugated to	10 µg
CRM_{197} protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide/LHD153R Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
LHD153R	12.5 µg
Sodium Chloride	3.4 mg
Histidine	0.1 mg
Tris	30 µg
Sterile water for injection, up to	0.5 ml
Group C (25 µg LHD153R) - MenC-CRM_{197}/Aluminium Hydroxide/LHD153R	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM_{197} protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide/LHD153R Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
LHD153R	25 µg
Sodium Chloride	3.4 mg
Histidine	0.2 mg
Tris	61 µg
Sterile water for injection, up to	0.5 ml

Group D (50µg LHD153R) - MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM$_{197}$ protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide/LHD153R Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
LHD153R	50 µg
Sodium Chloride	3.2 mg
Histidine	0.4 mg
Tris	121 µg
Sterile water for injection, up to	0.5 ml
Group E (100µg LHD153R) - MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM$_{197}$ protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg

Aluminum Hydroxide/LHD153R Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
LHD153R	100 µg
Sodium Chloride	2.9 mg
Histidine	0.8 mg
Tris	243 µg
Sterile water for injection, up to	0.5 ml

6.2 Non-Study Vaccines

The term 'non-study vaccine' refers to those vaccines which will be intentionally given to study subjects but not formally included in the analysis of study objectives.

No non-study vaccines are planned for this study. Any non-study vaccines administered during the study conduct will be captured in the eCRF as concomitant medications and/or vaccinations.

6.3 Vaccine Preparation and Administration

The investigator or designee will be responsible for oversight of the administration of vaccine to subjects enrolled in the study according to the procedures stipulated in this study protocol. All vaccines will be administered only by unblinded personnel who are qualified to perform that function under applicable local laws and regulations for the specific study site.

The vaccine components will be provided in 5 separate kits (i.e. onefor the control and one for each of the 4 dosage groups). The vaccine components must be mixed prior to vaccination taking into account the appropriate aseptic procedures. Detailed vaccine preparation and administration instructions, including the maximal administration period, will be provided to investigators prior to study start and must be filed in the Investigator Site File.

PRECAUTIONS TO BE OBSERVED IN ADMINISTERING STUDY VACCINE:

- Prior to vaccination, subjects must be determined to be eligible for study vaccination and it must be clinically appropriate in the judgment of the investigator to vaccinate. Eligibility for vaccination prior to first study vaccine administration is determined by evaluating the entry criteria outlined in protocol sections 4.0.

- Study vaccines must not be administered to individuals with known hypersensitivity to any component of the vaccines.

- Standard immunization practices are to be observed and care should be taken to administer the injection intramuscularly. Before administering vaccine, the vaccination site is to be disinfected with a skin disinfectant (e.g., 70% alcohol). Allow the skin to dry. **DO NOT inject intravascularly**.

- As with all injectable vaccines, trained medical personnel and appropriate medical treatment must be readily available in case of anaphylactic reactions following vaccine administration. For example, epinephrine 1:1000, diphenhydramine, and/or other medications for treating anaphylaxis should be available.

6.4 Misadministration of Vaccine

Misadministration is defined as receiving a dose of study vaccine that was not reconstituted as instructed or administered by a different route from the intended route of administration. An overdose of study vaccine (whether accidental or intentional) is defined as receiving more than the dosing quantities referred to in Table 6.1-1

Any misadministration or overdose of study vaccine detailed in this protocol must be treated as a serious adverse event (whether or not associated with an adverse experience) and reported as such within 24 hours to the Sponsor.

6.5 Prior and Concomitant Medications and Vaccines

All medications, vaccines and blood products taken or received by the subject within 180 days prior to the start of the study are to be recorded in the Prior and Concomitant Medications eCRF.

Medications taken for prophylaxis are those intended to prevent the onset of symptoms. Medications taken for treatment are intended to reduce or eliminate the presence of symptoms that are present.

The use of antipyretics and/or analgesic medications within 24 hours prior to vaccination must be identified and the reason for their use (prophylaxis versus treatment) must be described in the source document and/or Subject Diary and must be recorded in the eCRF as concomitant medications. NOTE: Use of antipyretics/analgesics within 24 hours prior to vaccine administration is a reason to delay study vaccination (see section 4.3)

Concomitant medications include all medications (including vaccines) taken by/administered to the subject at and after enrolment and must be documented in the Prior and Concomitant Medications eCRF.

When recording concomitant medications/vaccines, they should be checked against the study entry criteria in section 4.0, to ensure that the subject should be enrolled in the study.

6.6 Vaccine Supply, Labeling, Storage and Tracking

The Sponsor will ensure the following:

- Supply the study vaccines.
- Appropriate labeling of all study vaccines provided that complies with the legal requirements of each country where the study is to be performed.

The investigator must ensure the following:

- Acknowledge receipt of the study vaccines by a designated staff member at the site, including:
  - Confirmation that the vaccines were received in good condition
  - Confirmation to the Sponsor of the temperature range during shipment from the Sponsor to the investigator's designated storage location
  - Confirmation by the Sponsor that the vaccines are authorized for use.
- Proper storage of the study vaccines, including:
  - Storage in a secure, locked, temperature-controlled location.
  - Proper storage according to the instructions specified on the labels.
  - Appropriate record keeping and inventory of the study vaccines, including regular documentation of adequate storage temperature.
- Appropriate use of the study vaccines, including:
  - No use of vaccines prior to receipt of authorization for use from the Sponsor.
  - Use only in accordance with the approved protocol.
  - Proper handling, including confirmation that the vaccine has not expired prior to administration.

- Appropriate documentation of administration of vaccines to study subjects including:
    - Date, dosage, batch/lot numbers, expiration dates, unique identifying numbers assigned to subjects and study vaccines, and time of vaccine administration. This information will be maintained in an accountability log that will be reviewed by the site monitor.
    - Reconciliation of all vaccines received from the Sponsor. Reconciliation is defined as maintaining records of which and how many vaccines were received, which vaccines were administered to subjects, which vaccines were destroyed at the site, and which vaccines were returned to the Sponsor, as applicable.

- Proper adherence to the local institutional policy with respect to destruction of study vaccines.
- Complete record keeping of vaccine use, wastage, return or destruction, including documentation of:
    - Copy of the site's procedure for destruction of hazardous material.
    - Number of doses destroyed, date of destruction, destruction code (if available), method of destruction, and name of individual performing destruction.

Vaccines that have been stored differently from the manufacturer's indications **must not** be used unless the Sponsor provides written authorization for use. In the event that the use cannot be authorized, the Sponsor will make every effort to replace the vaccine supply. All vaccines used in conjunction with this protocol must be stored separately from normal hospital/practice stocks to prevent unintentional use of study vaccines outside of the clinical study setting.

Monitoring of vaccine accountability will be performed by the study monitor during site visits and at the completion of the study.

At the conclusion of the study, and as appropriate during the course of the study, the investigator must ensure that all unused study vaccines, packaging and supplementary labels are destroyed locally (upon approval from Sponsor) or returned to the Sponsor.

7.0 ASSESSMENTS

7.1 Safety Assessment

The measures of safety used in this study are based on previous study data and based on comparable routine clinical/laboratory procedures. They include a close vigilance for, and stringent reporting of selected local and systemic adverse events routinely monitored in vaccine studies as indicators of reactogenicity.

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

The period of observation for AEs extends from the time the subject signs informed consent until he or she completes the specified safety follow-up period (Day 366) or terminates the study early (whichever comes first). AEs occurring after the informed consent form is signed but prior to receiving study vaccine/product will be documented as an adverse event and recorded within the source documents. However, any AEs occurring prior to receipt of any study vaccine will be analyzed separately from “treatment emergent” AEs (AEs occurring after administration of the first study vaccine).

Adverse events are collected as either solicited or unsolicited adverse events. Solicited events are derived from organized data collection systems, such as Subject Diaries or interview.

7.1.1 Solicited Adverse Events

The term “reactogenicity” refers to solicited signs and symptoms (“solicited adverse events”) occurring in the hours and days following a vaccination, to be collected by the subject after the first 24 hours inpatient observation period at Day 1until Day 15, using a pre-defined Subject Diary.

The following solicited adverse events are included in the Subject Diary. Each adverse event is to be assessed using the scoring system shown in Appendix A (Solicited Local AEs) and Appendix B (Solicited Systemic AE):

Solicited Local Adverse Events

Solicited local AEs include:

- injection site erythema
- injection site induration
- injection site pain
- injection site swelling **Solicited Systemic Adverse Events**

Solicited systemic AEs include:

- body temperature ≥38.0°C (as measured orally)
- loss of appetite
- nausea
- fatigue
- generalized myalgia
- generalized arthralgia
- headache
- chills
- vomiting
- diarrhea
- generalized rash
- urticaria

Other Solicited Data

Other solicited data collected per Subject Diary include:

- Use of analgesics/antipyretics recorded as “absent” or “present” and summarized by “for treatment” or “for prophylaxis”
- Body temperature as recorded daily, ideally at same time, by the oral route

The study staff must review the data entered into the Subject Diary as described in sections 3.4.2 and 5.3.1.

NOTE: Any solicited adverse event that meets any of the following criteria must be entered into the subjects' source documents (see section 9.1) and also as an adverse event in the eCRF:

- Solicited local or systemic adverse event that continues beyond Day 15 after vaccination.
- Solicited local or systemic adverse event that leads to a visit to a healthcare provider (medically attended adverse event, see section 7.1.3).
- Solicited local or systemic adverse event leading to the subject withdrawing from the study or the subject being withdrawn from the study by the investigator (adverse event leading to withdrawal, see section 7.1.3).
- Solicited local or systemic adverse event that otherwise meets the definition of a serious adverse event (see section 7.1.4).

7.1.2 Unsolicited Adverse Events

An unsolicited adverse event is an adverse event that was not solicited using a Subject Diary and that was spontaneously communicated by a subject who has signed the informed consent.

7.1.3 Evaluation of Adverse Events

Every effort should be made by the investigator to evaluate safety information reported by a subject for an underlying diagnosis and to capture this diagnosis as the event in the AE page. In other words, the practice of reporting only symptoms (e.g., "cough" or "ear pain") are better reported according to the underlying cause (e.g., "asthma exacerbation" or "otitis media").

The severity of events reported on the Adverse Events CRF will be determined by the investigator as:

Mild: transient with no limitation in normal daily activity.
Moderate: some limitation in normal daily activity.
Severe: unable to perform normal daily activity.

The relationship of the study treatment to an AE will be determined by the investigator based on the following definitions:

1. Not Related

The AE is not related to an investigational vaccine if there is evidence that clearly indicates an alternative explanation. If the subject has not received the vaccine, the timing of the exposure to the vaccine and the onset of the AE are not reasonably related in time, or other facts, evidence or arguments exist that reasonably suggest an alternative explanation, then the AE is not related.

2. Possibly Related

The administration of the investigational vaccine and AE are considered reasonably related in time and the AE could be explained by exposure to the investigational vaccine or by other causes.

3. Probably Related

Exposure to the investigational vaccine and AE are reasonably related in time and no alternative explanation has been identified.

The relationship of the study treatment to an unsolicited AE will be determined by the investigator.

Note: solicited AEs will not be evaluated for relationship to study treatment. Grading for severity of solicited local and systemic AEs is described in section 7.1.1.

Adverse events will also be evaluated by the investigator for the co-existence of any of the other following conditions:

- "Medically attended adverse event": an adverse event that leads to a visit to a healthcare provider.
- "New onset of chronic disease" (NOCD): an adverse event that represents a new diagnosis of a chronic medical condition that was not present or suspected in a subject prior to study enrolment.
- AEs leading to withdrawal: adverse events leading to study or vaccine withdrawal.

All AEs, regardless of severity, will be monitored until resolution or until the investigator assesses them as chronic or stable. All subjects experiencing AEs - whether considered associated with the use of the study vaccine or not - must be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible.

7.1.4 Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose results in one or more of the following:

- Death.
- Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe.
- Required or prolonged hospitalization.
- Persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions).
- Congenital anomaly/or birth defect.
- An important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

Adverse events which do not fall into these categories are defined as non-serious.

It should be noted that a severe adverse event need not be serious in nature and that a serious adverse event need not, by definition, be severe.

Serious adverse events will be captured both on the Vaccines Serious Adverse Event (VSAE) form as well as on the AE CRF. All SAEs will be evaluated by the investigator for relationship of the event to study vaccine. SAEs that are judged to be possibly or probably related to the study vaccine should be reported to the Sponsor as related/suspected events.

The relationship of the study treatment to an SAE will be determined by the investigator based on the following definitions:

1. Related/suspected

The SAE is judged by the investigator to be possibly or probably related to the study vaccine on the AE CRF page (see section 7.1.3).

2. Not Related

The SAE is not related if exposure to the study vaccine has not occurred, **or** the occurrence of the SAE is not reasonably related in time, **or** the SAE is considered unlikely to be related to use of the study vaccine, i.e., there are no facts (evidence) or arguments to suggest a causal relationship.

The relationship of the study vaccine to an SAE will be determined by the investigator.

In addition, SAEs will be evaluated by the Sponsor or designee for "expectedness." An unexpected AE is one that is not listed in the current Summary of Product Characteristics or the Investigator's Brochure or an event that is by nature more specific or more severe than a listed event.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the Medical History CRF. If the onset of an event occurred before the subject entered the study (e.g., any pre-planned hospitalization for conditions like cosmetic treatments or for non-emergency routine visits for a pre-existing condition), the hospitalization would not lead to an AE being classified as serious unless, in the view of the investigator, hospitalization was prolonged as a result of participation in the clinical study or was necessary due to a worsening of the pre-existing condition.

7.1.4.1 Adverse Events of Special Interest

Certain adverse events of special interest (AESIs) are monitored for after the administration of immunostimulatory agents. All subjects enrolled in the study will be monitored for AESIs for the entire follow-up period. The AESIs will be defined according to MedDRA preferred terms. The investigator will be provided with a list of AESIs prior to study start. Receipt of this list will be documented and stored, along with the list of AESIs, in the Investigator Site File. During the course of the trial the list of AESIs may change. If this occurs, the investigators will be advised of the change and confirmation of receipt will be documented. The updated list of AESIs and documentation of receipt are also stored in the Investigator Site File. The occurrence of any of these adverse events will be treated as a serious adverse event (SAE), meeting the criterion of a "medically important event."

Subjects will be assessed for diagnosis of an AESI at the following visits:

- Pre-vaccination clinic visit (Day -21 to Day -3)
- Visit 1 (Day 1, pre-vaccination)

- Visit 2 (Day 4) - Visit 3 (Day 8)
- Visit 4 (Day 15)
- Visit 5 (Day 22; Safety Follow-Up Call)
- Visit 6 (Day 29) - Visit 7 (Day 85)
- Visit 8 (Day 113)
- Visit 9 (Day 181)
- Visit 10 (Day 209; Safety Follow-Up Call)
- Visit 11 (Day 271; Safety Follow-Up Call)
- Visit 12 (Day 366; Study Termination Visit)

At these visits a qualified health care practitioner listed on the site's responsibilities and delegation logs will conduct a review of organ systems and a targeted physical exam and will evaluate subjects for any new signs or symptoms that could indicate one of the AESIs as specified in the list of AESIs stored in the Investigator Site File. They will also interview the subject about recent medical history and any new diagnosis that could indicate an AESI. Medical records related to any new medical event or diagnosis will be requested, reviewed by the site staff, and recorded in the subject's source documents.

A diagnosis of an AESI will be reported in the same manner and time frame as an SAE using the VSAE form. The investigator must notify Novartis within 24 hours. The AESI diagnosis, as well as any medications taken to treat the condition, will be recorded in the subject's source documents and on the Adverse Events eCRF.

7.1.5 Methods for Recording Adverse Events and Serious Adverse Events

All findings regarding Adverse Events must be reported on an Adverse Events CRF and on the VSAE form, if applicable, which is part of the Investigator Site File. All findings in subjects experiencing AEs must be reported also in the subject's source document.

All SAEs which occur during the course of the study, whether considered to be associated with the study vaccination or not, must be reported **within 24 hours of the site becoming aware of the event** to Novartis or its designee. Specific instructions and contact details for collecting and reporting SAEs to Novartis will be provided to the investigator.

All SAEs are also to be documented on the Adverse Events CRF. Any medication or other therapeutic measures used to treat the AE will be recorded on the appropriate CRF(s) in addition to the outcome of the AE.

After receipt of the initial report, representatives of Novartis or its designee will contact the investigator if it is necessary to obtain further information for assessment of the event.

All SAEs must be reported by the investigator to his/her corresponding EC and applicable regulatory authorities in accordance with institutional policy/regulatory requirements and adequate documentation of this notification must be provided to the Sponsor.

Novartis or its designee must also comply with the applicable regulatory requirement(s) related to the reporting of suspected unexpected serious adverse vaccine reactions (also known as SUSARs) to the regulatory authority(ies) and the IRB/EC. If a SUSAR or other safety signal relating to use of one of the study vaccines is reported to Novartis or its designee, the Sponsor will communicate the information to the investigator and the investigator will be responsible for submitting this information to the EC and other relevant authorities.

7.1.5.1 Post-Study Events

Any suspected SAE that occurs outside of the protocol-specified follow-up period or after the end of the study but considered to be caused by the study vaccine must be reported to Novartis or its designee. These SAEs will be processed by Novartis or its designee as during the course of the study, until 3 months after the last scheduled study visit. Instructions and contact details for collecting and reporting these suspected SAEs will be provided to the investigator.

7.1.6 Pregnancies

To ensure subjects' safety, each pregnancy in a subject after study vaccination must be reported to Novartis within 72 hours of the site learning of its occurrence. If the subject agrees to submit this information, the pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if intended duration of safety follow-up for the study has ended.

Pregnancy data must be recorded on a Pregnancy Report CRF (initial report) and Pregnancy Follow-Up CRF (outcome report) and reported to Novartis. Instructions and contact details for submitting the Pregnancy CRFs will be provided to the investigator.

Any pregnancy outcome meeting the definition of a SAE (see section 7.1.4) must also be reported on the VSAE Report Form.

7.1.7 Safety Laboratory Measurements

Blood and urine samples will be collected from all subjects at the Pre-vaccination Screening, at Visit 1, at Visit 3 and at Visit 6 as outlined in Time and Events Table 3. The blood safety laboratory assessments will include sodium, potassium, bicarbonate, blood urea nitrogen, creatinine, liver function tests (ALT, AST), a complete blood count and Creactive protein. The urine safety laboratory assessments will include protein, glucose and red blood cells. An additional blood and urine sample will be collected in case of a clinic Early Termination Visit as outlined in section 5.5.1.

All testing will be conducted by qualified and certified laboratories. Abnormal laboratory values will be defined following the FDA CBER Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" dated September 2007, or the institution's normal ranges if they differ from CBER guidance. Please see Appendix C, D and E for further details on the Toxicity Grading Scales according to CBER.

Retesting may be performed in case of abnormal values per guidance of the investigator. Retest results will not be captured in the eCRF.

7.2 Efficacy Assessment

Efficacy measurement will not be performed as part of this study.

7.3 Immunogenicity Assessment

The measures to assess the primary and secondary immunogenicity endpoints for this study are standard, i.e., widely used and generally recognized as reliable, accurate, and relevant (able to describe the quality and extent of the immune response).

The assay's used in this study to assess the primary and immunogenicity endpoints are human serum bactericidal assay (hSBA) and ELISA specific for meningococcal serogroup C

The hSBA is a functional measure of the ability of specific antibodies, in conjunction with human complement, to kill meningococcal serogroup C indicator strains, and is widely used and generally recognized as the serological correlate of protection. The specific ELISA will be used to measure the induction of antibodies directed against meningococcal serogroup C following vaccination with the study vaccines.

Blood samples (approximately 10 ml) to obtain serum for hSBA and ELISA assays will be collected at Day 1, Day 8, Day 29 and Day 181 (refer to section 3.5 for detailed specimen collection procedures).

Testing will be conducted by a Novartis or designated laboratory in a blinded manner towards the treatment group. Laboratory contact details are listed in the Protocol Ancillary Document.

All data will be captured at the laboratory and transferred via Electronic Data Transfer (EDT)

Details on all blood sample handling steps are described in the Clinical Specimen Lab Manual provided to the study site.

7.4 Exploratory Measurements

In those subjects who agree to a separate Informed Consent, additional blood samples will be collected at Day 1, Day 4, Day 8, Day 29 and Day 181 for exploratory measurements. The purpose of these exploratory measurements is to assess the systemic exposure of LHD153, to further delineate vaccine induced antigen specific immune responses and to evaluate biomarkers that may be predictive for safety and/or innate immune activation.

All exploratory measurements will be conducted by a Novartis or a designated laboratory. Laboratory contact details are listed in the Protocol Ancillary Document.

Exploratory measurements may be performed after the Clinical Study Report (CSR) has been completed, in which case these data will be submitted as an addendum to the CSR.

Systemic exposure of LHD153R

Systemic exposure of LHD153 will be assessed by analyzing LHD153 blood plasma levels at Day 1 (baseline, 1, 2, 4, 8 and 24h after vaccination) and Day 4 using LC/MS/MS. Time-points for assessment of clinical exposure of LHD153 have been selected based on non-clinical data in dogs and rats.

Vaccine-induced antigen-specific immune responses

The frequency of B cells specific for MenC polysaccharide and CRM_{197} will be determined by enzyme-linked immunosorbent spot (ELISPOT) at Day 1, Day 8, Day 29 and Day 181 in order to evaluate the baseline specific B-cell frequency (Day 1), the peak of plasmablast responses (Day 8), the peak of B cell memory responses (Day 29), and the persistence of memory B cell responses (Day 181).

Subsequently, the diversity of the antigen specific B-cell repertoire as well as the specific antibody functionality will be analyzed in a selected subset of subjects. The selection of the subset will be based on the most pronounced response to the study vaccines when compared to baseline as determined by the primary and secondary immunogenicity assessment.

The diversity of the elicited B-cell receptors will be assessed through sequence analysis of complementary DNA (cDNA) generated from immunoglobulin (Ig) messenger RNA (mRNA). The Ig cDNAs will be analyzed from antigen-specific B cells obtained at Day 1, Day 29 and/or Day 181 and plasmablasts isolated at Day 8. The analysis of the B-cell receptor diversity does not have the intent nor the capability to identify or rule out any genetic modifications in the RNA or DNA that are presumably linked to disease or predisposition to disease.

To evaluate the functionality specific antibodies induced by the study vaccines, biochemical and cell-based assays will be performed on a selected subset of serology samples collected for the assessment of the primary and secondary immunogenicity endpoints at Day 1, Day 8, Day 29 and Day 181. The evaluation of antigen specific antibody functionality includes determination of the antibody isotype and the antibody glycosylation state. Furthermore, the ability of the MenC-specific antibodies to fix complement, to promote antibody-dependent cell mediated cytoxicity (ADCC), to induce phagocytosis and to activate FcR+ cells in vitro will be assessed. If the quantity of serum available for this specific exploratory objective is limited, assessments of isotype, glycosylation state and complement fixing capacity will be prioritized over the other assessments.

The frequency of T cells specific for the CRM_{197} protein at baseline (Day 1), at Day 8 and at Day 29 after vaccination with the study vaccines will be determined by FACS analysis using intracellular staining with a wide panel of cytokines and surface markers to identify cell populations.

Early Markers for Safety and Innate immune activation

The evaluation of potential biomarkers of safety and innate immune activation will be performed on blood specimens collected at Day 1 (baseline, 6h and 24h after vaccination) and Day 4.

The vaccine-induced production of inflammatory cytokines and chemokines will be monitored on serum samples using a commercially available multiplex ELISA assay for a panel of pro-inflammatory cytokines and chemokines, including Eotaxin, Eotaxin-3, GMCSF, IFN-g, IL-1a, IL-1b, IL-10, IL-12 p70, IL-12/IL-23p40, IL-13, IL-15, IL-16,

IL17A, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-8 (HA), IP-10, MCP-1, MCP-4, MDC, MIP1a, MIP-1b, TARC, TNF-a, TNF-b, VEGF.

The vaccine-induced expression of genes and gene families will be monitored on whole blood samples using of RNA microarrays by existing technologies The RNA micro array analysis does not have the intent nor the capability to identify or rule out any genetic modifications in the RNA or DNA that are presumably linked to disease or predisposition to disease.

8.0 STATISTICAL CONSIDERATIONS

8.1 Endpoints

8.1.1 Primary Endpoint(s)

8.1.1.1 Primary Safety Endpoint(s)

The measures for assessing safety and tolerability (by vaccine group within each cohort and by LHD153R adjuvant dosage group overall) are as follows:

- The frequency and percentage of subjects with solicited local and systemic AEs through Day 15. Time intervals after vaccination that will be summarized are:30 minutes post-vaccination, Days 1-4 (without 30 minutes), Days 5-8, Days 8-15, Days 1-8 (without 30 minutes) and Days 1-15 (without 30 minutes).
- The frequency and percentage of subjects with any unsolicited AEs from the day of vaccination (Day 1) to Day 15.
- The frequency and percentage of subjects with SAEs, medically attended AEs, AEs leading to study withdrawal, NOCDs, AESIs for the following time periods: day of signed informed consent until study completion (Day 366), day of vaccination (Day 1) to Day 29 and Day 29 to study completion (Day 366).
- The absolute values and changes in hematology, chemistry, and urinalysis parameters (see section 7.1.7).
- The frequency and percentage of subjects with abnormal laboratory parameter values

as classified by investigator normal ranges (low, normal, high) and as classified by CBER toxicity grading scales, when available.

8.1.1.2 Primary Efficacy Endpoint(s)

Not applicable.

8.1.1.3 Primary Immunogenicity Endpoint(s)

The primary immunogenicity endpoints are the GMTs measured by hSBA directed against *N. meningitidis* serogroup C from samples collected on Day 1 (baseline, before vaccination) and Day 29 as well as the GMR of the titers (Day 29 / Day 1).

8.1.2 Secondary Endpoint(s)

8.1.2.1 Secondary Safety Endpoint(s)

Not applicable.

8.1.2.2 Secondary Efficacy Endpoint(s)

Not applicable.

8.1.2.3 Secondary Immunogenicity Endpoint(s)

The secondary immunogenicity endpoints are:

- the GMTs and corresponding GMRs measured by hSBA directed against *N. meningitidis* serogroup C for samples collected at Day 8 and Day181.
- the percentage of subjects with hSBA seroresponse at Days 8, 29, and 181. seroresponse is defined as a post vaccination hSBA ≥8 for subjects with a baseline hSBA <4 or have an increase of at least 4 times the baseline hSBA level for subjects with pre-vaccination hSBA ≥4.
- Antibody geometric mean concentrations (GMCs) against *N. meningitidis* serogroup C measured by ELISA for samples collected on Days 1 (baseline, prior to vaccination), 8, 29 and 181.
- The percentage of subjects with at least a 4-fold increase in antibody concentrations to *N. meningitidis* serogroup C as measured by ELISA on Day 8, 29 and 181 relative to baseline (Day 1)

8.1.3 Exploratory Endpoint(s)

The exploratory endpoints are based on results of testing which may not be performed until after the study report has been finalized and will be further refined prior to testing. They include the following:

- Serum concentration of LHD153 at Day 1 baseline (prior to vaccination), Day 1 (1h , 2h, 4h, 8h and 24h after vaccination), Day 4 by LC-MS/MS.
- Frequency of meningococcal C polysaccharide-specific and CRM_{197}-specific B cells at Day 1 (baseline), Day 8, Day 29 and Day 181 by ELISPOT.
- Diversity of the meningococcal C polysaccharide-specific B-cell repertoire at Day 1 (baseline), Day 8, Day 29, and Day 181 by immunoglobulin cDNA sequencing.
- Functionality of antigen specific antibodies will be assessed at Day 1 (baseline), Day 8, Day 29 and Day 181 by analysis of immunoglobulin isotype, glycosylation state and their ability to fix complement, promote antibody-dependent cell mediated cytoxicity, induce phagocytosis and activate FcR+ cells. If the quantity of serum available for this specific exploratory objective is limited, assessments of isotype, glycosylation state and complement fixing capacity will be prioritized over the other assessments.
- Frequency and quality of T cells specific for CRM_{197} at Day 1 (baseline), Day 8 and Day 29 by fluorescence activated cell sorting (FACS) analysis using intracellular staining with a wide panel of cytokines and surface markers to identify cell populations.
- Serum concentrations of a panel of 30 chemokines and cytokines at Day 1 (baseline), Day 1 (6h and 24h after vaccination), Day 4 and Day 8 by multiplex Electro-chemoluminescence based assay.
- Gene expression profile in whole blood at Day 1 (baseline), Day 1 (6h and 24h after vaccination), Day 4 and Day 8 by RNA micro array analysis

8.2 Success Criteria

The study has no formal statistical hypotheses and will not be declared positive or negative according to given rules. The selection of an appropriate LHD153R adjuvant dosage for future studies will be determined by the joint evaluation of the

immunogenicity and safety profiles of each dosage group. **8.2.1**

Success Criteria for Primary Objective(s) Not applicable.

8.2.2 Success Criteria for Secondary Objective(s)

Not applicable.

8.3 Analysis Sets

8.3.1 All Enrolled Set

All screened subjects who provide informed consent and provide demographic and/or baseline screening assessments, regardless of the subject's randomization and treatment status in the study and received a Subject ID.

8.3.2 All Exposed Set

All subjects in the enrolled set who receive a study vaccination.

8.3.3 Safety Set

Safety Set (solicited adverse events and other solicited reactions)

All subjects in the Exposed Set who:

- Provide post vaccination reactogenicity data.

Safety Set (unsolicited adverse events)

All subjects in the Exposed Set who:

- Have post-vaccination unsolicited adverse event records.

Safety Set (overall)

All subjects in the Exposed Set who:

- Have either post-vaccination adverse event or reactogenicity records.

Subjects will be analyzed as "treated" (i.e., according to the vaccine a subject received, rather than the vaccine to which the subject may have been randomized).

8.3.4 Full Analysis Set (FAS) Efficacy/Immunogenicity Set

All subjects in the Enrolled Set who:

- Receive a study vaccination AND provide efficacy/immunogenicity data at relevant time points.

FAS sets will be analyzed “as randomized” (i.e., according to the vaccine a subject was designated to receive, which may be different from the vaccine the subject actually received).

8.3.5 Per Protocol (PP) Set Efficacy/Immunogenicity Set

All subjects in the FAS efficacy/immunogenicity set who:

- Are not excluded due to reasons (see section 8.3.8) defined prior to unblinding or analysis.

PPS are subsets of FAS and should always be defined even if the objectives do not require it.

Examples for subjects excluded due to other reasons than protocol deviations are:

- Subjects who withdrew informed consent.
- Premature withdrawal due to an adverse event.

Exclusions need to be considered by objective/time point, i.e., sometimes not all data of a subject but only part of the subject's data will be removed from the PPS analysis.

8.3.6 Other Analysis Sets

All subjects in the Enrolled Set who consent to additional blood draws, receive a study vaccination AND provide exploratory assay data at relevant time points will be included in an exploratory assay subset.

8.3.7 Subgroups

Selected immunogenicity analyses may be provided based on seropositivity status at baseline.

8.3.8 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. A protocol deviation may be a reason to remove data from an analysis set at the time of analysis. Reportable protocol deviations will be defined as exclusionary from the analysis according to protocol objectives and endpoints, which will

be specified in the statistical analysis plan. In some cases exclusion of data may be due to a reason other than a protocol deviation, e.g. early termination.

8.4 Statistical Analysis Plan

This section provides a summary of the statistical methodology to be used. A more detailed description of analysis methods will be provided in a separate statistical analysis plan which may also include additional exploratory analyses not explicitly mentioned in the following sections.

8.4.1 Analysis of Demographic and Baseline Characteristics

Descriptive statistics (number of non-missing observations, mean, standard deviation, median, minimum and maximum) for age, height and weight at enrolment will be calculated overall and by vaccine group and LHD153R adjuvant dosage.

Distributions of subjects by sex and ethnic origin will be summarized overall and by vaccine group and LHD153R adjuvant dosage.

8.4.2 Analysis of Primary Objective(s)

8.4.2.1 Analysis of Primary Safety Objective(s)

Safety of the study vaccines will be assessed in all subjects in terms of the frequency and percentage of reported AEs as well as by changes in clinical laboratory values.

8.4.2.1.1 Analysis of Extent of Exposure

The frequency and percentage of subjects with vaccinations will be summarized by vaccine group and LHD153R adjuvant dosage, by cohort and overall, for the Enrolled Set.

8.4.2.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events

All solicited adverse events will be summarized according to defined severity grading scales. Use of medication to prevent/treat fever will be summarized according to frequencies and percentages reporting “Yes” and “No”.

Frequencies and percentages of subjects experiencing each adverse event will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic adverse event overall and at each time point will also be presented.

Post-vaccination solicited adverse events reported from Day 1 to Day 15 will be summarized for the intervals Day 1-4 (without 30 minutes), Day 5-8, Day 1-8 (without 30 minutes), Day 8-15 and Day 1-15 (without 30 minutes) by maximal severity and by vaccine group and LHD153R adjuvant. The severity of solicited local adverse events, including injection-site erythema, swelling and induration will be summarized according to categories based on linear measurement: 25 to 50 mm, 51-100 mm, > 100 mm.

Injection site pain and systemic reactions (except fever) occurring up to Day 15 will be summarized according to “mild”, “moderate” or “severe”.

Each solicited local and systemic adverse event will also be further summarized as “none” versus “any”.

Implausible measurements (for further definition see statistical analysis plan) will be left out of the analysis.

Use of antipyretics and analgesics will be summarized by frequency by type of use (prophylactic versus treatment) and percentage of subjects reporting use. The influence of antipyretics and analgesics use on the occurrence of specific adverse events (e.g., fever, pain) will be assessed.

Body temperature will be summarized by 0.5 °C and 1.0 °C increments from 36.0 °C up to ≥40 °C.

8.4.2.1.3 Analysis of Unsolicited Adverse Events

This analysis applies to all adverse events occurring during the study, judged either as probably related, possibly related, or not related to vaccination by the investigator, recorded in AE CRF, with a start date on or after the date of first vaccination. AE starting prior to the first vaccination will only be listed. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class.

All reported adverse events, as well as adverse events judged by the investigator as at least possibly related to study vaccine, will be summarized according to system organ class and preferred term within system organ class. These summaries will be presented by vaccination group and LHD153R adjuvant dosage for each cohort and by interval of study observation. When an adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted.

Separate summaries will be produced for the following categories:

- Serious adverse events.
- Adverse events that are possibly or probably related to vaccine.
- Adverse events of special interest.
- New onset of chronic disease.
- Adverse event leading to withdrawal.
- Adverse events leading to a medically attended visit.
- Adverse event by data source.

Data listings of all adverse events will be provided by subject. In addition, adverse events in the categories above will be provided as listed data.

8.4.2.1.4 Analysis of Safety Laboratory Values

The investigator must review all safety laboratory results (see Section 7.1.7). Abnormal laboratory values and clinically significant changes in values from pre-vaccination (Screening Visit) will be assessed, using medical judgment, based on the FDA CBER Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" dated September 2007, or the institution's normal ranges if they differ from CBER guidance. Please see Appendix C, D and E for further details.

The following information will be provided:

- Change in absolute laboratory value from pre-vaccination (Screening Visit) to Day 8 (Visit 3) and Day 29 (Visit 6) after vaccination
- The classification of laboratory values and/or their changes from pre-vaccination according to the CBER toxicity grading scale
- 3 x 3 shift tables by visit using the categorization of laboratory values according to institutional normal reference ranges (below, within, above)

8.4.2.2 Analysis of Primary Efficacy Objective(s)

Not applicable.

8.4.2.3 Analysis of Primary Immunogenicity Objective(s)

8.4.2.3.1 Statistical Hypotheses

There are no statistical hypotheses associated with the secondary immunogenicity objectives. All analyses are descriptive.

8.4.2.3.2 Analysis Sets

The primary immunogenicity analyses will be based on the per-protocol set (PPS) at Day 29. The primary analyses will be repeated using the Full Analysis Set (FAS) as a measure of the sensitivity/robustness of the results (further details are given in section 8.3).

8.4.2.3.3 Statistical Methods

Before any statistical analysis that assumes normally distributed observations, antibody titers will be $\log_{10}$-transformed. Individual titers below the limit of quantitation (LLQ) will be set to half that limit.

Geometric Mean Titers

The logarithmically (base 10) transformed antibody titers will be modeled using an analysis of covariance (ANCOVA) model with a qualitative factor for LHD153R adjuvant dosage (0 [for unadjuvanted MenC], 12.5, 25, 50 or 100 µg) and log (base 10) pre-vaccination titer as a covariate. The adjusted GMT and the two-sided, 95%, confidence intervals (CIs) of the GMT will be calculated based on this model as will the ratio of GMTs and corresponding CIs. The adjusted GMT and two-sided 95% CIs will be constructed by exponentiation (base 10) of the least square means of the logarithmically transformed (base 10) antibody titer. The ratio of GMTs (LHD153R adjuvant dosage minus Men C), and corresponding two-sided 95% CIs, will be constructed by exponentiation (base 10) of the least square differences obtained from this model. The model can be written as:

$$\log_{10}(y_{ik}) = \mu + \alpha_i + \beta x_{ik} + \varepsilon_{ik}$$

where μ represents a common overall mean, α_i represents the adjuvant dose group i effect, β represents the common slope for the log10 pre-vaccination titer, x_{ik} for subject k in adjuvant dose group I, and ε_{ik} represents random error for subject k in adjuvant dose group i.

Geometric Mean Ratios

The logarithmically (base 10) transformed within subject ratio of antibody titers (Day 29 / pre-vaccination) will be modeled using an analysis of variance model with a qualitative

factor for LHD153R adjuvant dosage (0 [for non-LHD153R adjuvanted MenC], 12.5, 25, 50 or 100 µg). The adjusted GMR and the two-sided, 95% CIs of the GMR will be calculated based on this model. The model can be written as:

$\log_{10}(y_{ik}) = \mu + \alpha_i + \varepsilon_{ik}$

where μ represents a common overall mean, α_i represents the adjuvant dose group i effect and ε_{ik} represents random error for subject k in adjuvant dose group i.

Handling of missing values

For immunogenicity data, it may be reasonable to consider missing immunogenicity values as missing completely at random (MCAR), i.e., not informative. Therefore, the primary analysis will comprise a complete case analysis only, without introducing any bias. Imputation methods will not be used.

8.4.3 Analysis of Secondary Objective(s) 8.4.3.1

Analysis of Secondary Safety Objective(s) Not

applicable.

8.4.3.2 Analysis of Secondary Efficacy Objective(s)

Not applicable.

8.4.3.3 Analysis of Secondary Immunogenicity Objective(s)

8.4.3.3.1 Statistical Hypotheses

There are no statistical hypotheses associated with the secondary immunogenicity objectives. All analyses are descriptive.

8.4.3.3.2 Analysis Sets

The secondary immunogenicity analyses will be based on the PPS (further details are given in section 8.3) or the appropriate subset of subjects.

8.4.3.3.3 Statistical Methods

The secondary immunogenicity endpoints are:

- the GMTs and corresponding GMRs measured by hSBA directed against *N. meningitidis* serogroup C for samples collected at Day 8 and Day181.
- the percentage of subjects with hSBA seroresponse at Days 8, 29, and 181. seroresponse is defined as a post vaccination hSBA ≥8 for subjects with a baseline hSBA <4 or have an increase of at least 4 times the baseline hSBA level for subjects with pre-vaccination hSBA ≥4.
- Antibody geometric mean concentrations (GMCs) against *N. meningitidis* serogroup C measured by ELISA for samples collected on Days 1 (baseline, prior to vaccination), 8, 29 and 181.
- The percentage of subjects with at least a 4-fold increase in antibody concentrations to *N. meningitidis* serogroup C as measured by ELISA on Day 8, 29 and 181 relative to baseline (Day 1)

The GMTs for samples collected at Day 8 and Day 181 as well as the GMCs for samples collected at Day 1, Day 8, Day 29 and Day 181 will be analyzed using the same approach as for the primary immunogenicity endpoint.

The remaining immunogenicity endpoints are based on subjects meeting criteria for seroconversion or achieving a certain threshold value. These endpoints will be summarized using frequencies and percentages by LHD153R adjuvant dosage (0 [for non-LHD153R adjuvanted MenC], 12.5, 25, 50 or 100 µg). Two-sided 95% ClopperPearson CIs will also be provided for percentages. For analyses of seroconversion, separate summaries may be provided based on seropositivity status at baseline.

8.4.4 Analysis of Exploratory Objectives

Testing and analyses of exploratory endpoints may be performed after the Clinical Study Report (CSR) has been completed, in which case these data will be submitted as an addendum to the CSR.

In general, concentration and titer results will be summarized for each LHD153R adjuvant dosage group using geometric means and associated 2-sided 95% confidence intervals; and, categorical data will be summarized using frequencies and percentages, with corresponding two-sided, 95% confidence intervals. Full details of the analysis will be described in an amendment/addendum to the SAP.

8.5 Sample Size and Power Considerations of Primary Objectives

Sample size is not driven by statistical assumptions for formal hypothesis testing, but was based on the safety objective for the study. The table below provides the probability for various combinations of sample size (N) and presumed true frequency of a given event within an individual vaccine group

Frequency of Event	Probability to Observe at Least 1 Subject with a Given Event For Various Choices of N			
	4	**8**	**12**	**16**
0.05	0.1855	0.3366	0.4596	0.5599
0.10	0.3439	0.5695	0.7176	0.8147
0.15	0.4780	0.7275	0.8577	0.9257
0.20	0.5904	0.8322	0.9313	0.9718
0.30	0.8250	0.9423	0.9862	0.9967
0.40	0.8704	0.9832	0.9978	0.9997

The proposed combinations of sample sizes within each cohort are 4 aluminium hydroxide adjuvanted MenC-CRM$_{197}$ and 16 MenC-CRM$_{197}$ plus an assigned-level of LHD153R adsorbed to aluminium hydroxide. If all four cohorts are fully enrolled, there will be 16 subjects receiving aluminium hydroxide adjuvanted MenC-CRM$_{197}$.

With 16 subjects, events which occur at a frequency of 15% or more will be detected with at least 90% probability; and, events which occur at a frequency of 10% or more will be detected with 81% probability. With 4 subjects, events which occur at a frequency of 30% or more will be detected with at least 80% probability. Intermediate values of 8 and 12 are provided to correspond to sample sizes in the MenC- CRM$_{197}$ after cohort 2 and cohort 3 are fully enrolled.

8.6 Interim Analysis

The DMC will be reviewing the accumulating safety data from the study in order to continue enrollment of subjects within a cohort and whether to enroll subjects into the next cohort.

In addition to these periodic reviews, there will be a safety and immunogenicity interim analysis for the selection of an LHD153R adjuvant dosage based on the data collected through Day 29 from subjects enrolled in all cohorts. This analysis will be performed by personnel not involved in study decisions. The results will be unblinded at the group level

thereby preserving the blind for individual subjects. No adjustment to the overall alpha will be performed as the data collected subsequent to this analysis involve secondary and exploratory endpoints.

9.0 SOURCE DOCUMENTATION, STUDY MONITORING AND AUDITING

Study monitoring and auditing will be standardized and performed in accordance with the Sponsor's or delegated contract research organization's (CRO) standard operating procedures and applicable regulatory requirements (e.g., FDA, EMA, and ICH guidelines).

Prior to enrolment of the first study subject, Novartis or delegate will train investigators and/or their study staff on the study protocol, all applicable study procedures, documentation practices and all electronic systems. CRFs supplied by the Sponsor must be completed for each enrolled subject (see section 8.3.1 for definition of enrolled subject). Documentation of screened but not enrolled subjects must be maintained at the site and made available for review by the site monitor. Data and documents will be checked by the Sponsor and/or monitor.

9.1 Source Documentation

Prior to the start of the study, the site staff participating in the study conduct will be instructed on what documents will be required for review as source documents. The kinds of documents that will serve as source documents will be agreed between Sponsor or delegate and investigator and designees and specified in the SDA prior to subject enrolment.

In addition, source documentation **must** include all of the following: subject identification (on each page), eligibility and participation, proper informed consent procedures, dates of visits, adherence to protocol procedures, adequate reporting and follow-up of adverse events, documentation of prior/concomitant medication/vaccines, study vaccine receipt/dispensing/return records, study vaccine administration information, any data collected by a telephone conversation with the subject and date of completion and reason.

The subject must also allow access to the subject's medical records. Each subject must be informed of this prior to the start of the study and consent for access to medical records may be required in accordance with local regulations.

All safety data reported by subjects must be written down in source documents prior to entry of the data into CRFs. If there are multiple sources of information (e.g., Subject Diary, verbal report of the subject, telephone contact details, medical chart) supporting the diagnosis of an adverse event, these sources must be identified in the source documents, discrepancies between sources clarified, the ultimate diagnosis must be

justified and written in the source documents, and this diagnosis must be captured in the Adverse Event CRF (AE CRF). The AE CRF must also capture which source(s) of information were used to determine the adverse event (e.g., subject recall, medical chart, Subject Diary).

9.2 Study Monitoring, Auditing and Source Data Verification

Prior to enrolment of the first study subject, Novartis or its designee (e.g., a CRO) will develop a Monitoring Plan to specify how centralized and/or on-site monitoring, including clinical specimens reconciliation, will be performed for the study. Study progress will be monitored by Novartis or its designee as frequently as necessary to ensure:

- that the rights and well-being of human subjects are protected,
- the reported study data are accurate, complete, and verifiable from the source documents and
- the conduct of the study is in compliance with the current approved protocol/amendment(s), GCP and applicable regulatory requirements.

Contact details for the Novartis team or its designee involved in study monitoring will be provided to the investigator. Study data recorded on CRFs will be verified by checking the CRF entries against source documents in order to ensure data completeness and accuracy as required by study protocol.

Additional documents such as the investigator site file, pharmacy records, and informed consent documentation must also be available for review if requested. Arrangements for monitoring visits will be made in advance in accordance with the monitoring plan, except in case of emergency.

The investigator and/or site staff must make source documents of subjects enrolled in this study available for inspection by Novartis or its representative at the time of each monitoring visit and Sponsor audits, when applicable. These documents must also be available for inspection, verification and copying, as required by regulations, by officials of the regulatory health authorities (e.g., FDA, EMA and others) and/or ECs/IRBs. The investigator and study site staff must comply with applicable privacy, data protection and medical confidentiality laws for use and disclosure of information related to the study and enrolled subjects.

10.0 DATA MANAGEMENT

10.1 Data Entry and Management

In this study, all clinical data (including, but not limited to, AE/SAEs, concomitant medications, medical history, and physical assessments), safety data, and immunogenicity data will be entered into an EDC system, which is compliant with Title 21 Part 11 policies of the Code of Federal Regulations (FDA, 1997). The data system includes password protection and internal quality checks. The EDC system will be designed and validated by the Sponsor prior to activation for data entry by sites. The investigator or designated delegate must review data entered and electronically sign the CRFs to verify their accuracy.

Access to the EDC system for data entry or review will require training and distinct individual access code assignments to those site staff members who will be entering study data and those involved in study oversight who may review study data. Data are collected within the EDC system, to which the Sponsor and site monitors have exclusively "read only" access.

Three-part "no carbon required" (NCR) paper CRFs will be provided for each pregnant subject by the Sponsor. All appropriate pregnant subject data collected will be recorded on this form. One copy must be retained by the investigator, and all other copies (including the original copy) will be returned as directed by the Sponsor. Instructions on how to complete this form will be provided to the investigator.

10.2 Data Clarification

As part of the conduct of the trial, the Sponsor may have questions about the data entered by the site, referred to as queries. The monitors and the Sponsor are the only parties that can generate a query. All corrections and clarifications will be entered into the EDC system and will be identified by the person entering the information, the reason for the change, as well as the time of the changes made. If changes are made to a previously and electronically signed CRF, the investigator must confirm and endorse the changes

10.3 Data Protection

Novartis respects the subjects' rights to privacy and will ensure the confidentiality of their medical information in accordance with all applicable laws and regulations.

The Sponsor as Data Controller according to the European Directive on the protection of individuals with regard to the processing of personal data and on the free movement of such data (95/46/EC) confirms herewith compliance to Directive 95/46/EC in all stages of Data Management.

11.0 RECORD RETENTION

Investigators must retain all study records required by Novartis and by the applicable regulations in a secure and safe facility. The investigator must consult a Novartis representative before disposal of any study records, and must notify the Sponsor of any change in the location, disposition, or custody of the study files. Essential documents must be retained for 15 years. “Essential documents” are defined as documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. These documents should be retained for a longer period, however, if required by the applicable national regulatory or institutional requirements.

These principles of record retention will also be applied to the storage of laboratory samples, provided that the integrity of the stored sample permits testing.

12.0 USE OF INFORMATION AND PUBLICATION

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov, and in compliance with current regulations.

Novartis also assures that key results of this clinical study will be posted in a publicly accessible database within the required time-frame from the End of Study as defined in section 3.9.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Novartis personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Novartis personnel.

Novartis must be notified of any intent to publish data collected from the study and prior approval from Novartis must be obtained prior to submission for publication.

13.0 ETHICS

13.1 Regulatory and Ethical Compliance

The study will be conducted in compliance with the protocol, GCP and applicable regulatory requirement(s).

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, European Directive 2001/20/EC, Novartis codes on protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki (European Council 2001, US Code of Federal Regulations, ICH 1997).

13.2 Informed Consent Procedures

Eligible subjects may only be included in the study after providing written informed consent or assent, as described in section 5.1.1. Before the start of the study, the investigator will have the informed consent and any other materials that will be provided to the subjects reviewed and approved by the IRB/EC. This review and approval will be documented and stored with other study documents. The investigator or designee must fully inform the subject or legal guardian of all pertinent aspects of the study. A copy of the written informed consent will be given to the subject or the designee. The subject/designee must be allowed ample time to ask about the details of the study and to make a decision as to whether or not to participate in the study. The subject and/or legal guardian(s) **must** sign the consent form indicating their agreement to participate in the study before any study-related procedures are conducted. The informed consent process may be conducted up to 23 days prior to vaccination on Day 1. If the subject is unable to read and write, a witness must be present during the informed consent discussion and at the time of informed consent signature.

Prior to the start of the study, Novartis will provide to investigators a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/EC and a copy of the approved version must be provided to the Novartis monitor after IRB/EC approval.

Women of childbearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception

requirements indicated in the protocol for the duration of the study. In case of doubt on the ability of a subject to adhere to these requirements, that subject should not be allowed in the study

13.3 Responsibilities of the Investigator and IRB/EC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB/EC before study start. Properly constituted IRB/EC is defined in ICH Guideline for Good Clinical Practice E6 (R1), Section 3 (ICH, 1997). A signed and dated statement that the protocol and informed consent have been approved by the IRB/EC must be given to Novartis before study initiation. Prior to study start and at any time the protocol is amended during study conduct, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/ECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

The investigator also responsible for the following:

- Maintaining a list of appropriately qualified persons to whom the investigator has delegated significant study-related duties.
- Demonstrating the capability of recruiting the required number of suitable subjects within the recruitment period.
- Demonstrating sufficient time and staffing to properly conduct and complete the study within the agreed study period.
- Ensuring that all persons assisting with the study are adequately informed about the protocol, the investigational product(s), and their study-related duties and functions
- Ensuring that appropriately trained health care professionals are responsible for all study-related medical decisions and for ensuring appropriate medical care of subjects experiencing any adverse event related to the study.
- If permission to do so is given by the subject, ensuring that the subject's primary healthcare provider is informed of the subject's participation in the study.

The investigator should not implement any deviation from, or changes of the protocol without agreement by the Sponsor and prior review and documented approval/favourable

opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone number(s)). In addition, the investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to study subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

(a) to the IRB/IEC for review and approval/favourable opinion,

(b) to the Sponsor for agreement and, if required,

(c) to the regulatory authority(ies).

13.4 Protocol Amendments

An amendment is a written description of change(s) to or formal clarification of a study protocol which may impact on the conduct of the clinical study, potential benefit of the clinical study, or may affect subject safety, including changes of study objectives, study design, subject population, sample sizes, study procedures, or significant administrative aspects. An administrative change of a study protocol is a minor correction or clarification that has no significant impact on the way the clinical study is to be conducted and no effect on subject safety (e.g., change of telephone number(s), logistical changes). Protocol amendments must be approved by Novartis, health authorities where required, and the IRB/EC. In cases when the amendment is required in order to protect the subject safety, the amendment can be implemented prior to IRB/EC approval. Notwithstanding, the need for formal approval of a protocol amendment, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action, the IRB/EC at the study site, and, if required by local regulations, the relevant health authority should be informed within 10 working days.

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APPENDIX A: GRADING SCALES FOR SOLICITED LOCAL ADVERSE EVENTS

Adverse event Following Administration of Injectable Product	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Pain	present but does not interfere with activity	interferes with activity	prevents daily activity
Induration / Swelling / Erythema	25 – 50 mm	51 – 100 mm	> 100 mm

APPENDIX B: GRADING SCALES FOR SOLICITED SYSTEMIC ADVERSE EVENTS

Systemic Adverse event		Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Fever	**°C**	38.0 – 38.4	38.5 – 38.9	39.0 – 40
	°F	100.4 – 101.1	101.2 - 102	102.1 - 104
Chills		present but does not interfere with activity	interferes with activity	prevents daily activity
Loss of Appetite		Loss of appetite without decreased oral intake	decreased oral intake without weight loss	decreased oral intake with weight loss
Nausea		Nausea present but not interfering with oral intake	Nausea leading to decreased oral intake	Nausea leading to minimal to no oral intake
Vomiting		1-2 episodes/24 hours	>2 episodes/24 hours	requires outpatient hydratation
Diarrhea		2-3 loose stools /24 hours	4-5 loose stools /24 hours	6 or more watery stools /24 hours or requires outpatient IV hydration
Generalized Myalgia		present but does not interfere with activity	interferes with activity	prevents daily activity
Generalized Arthralgia		present but does not interfere with activity	interferes with activity	prevents daily activity
Headache		present but does not interfere with activity	interferes with activity	prevents daily activity
Fatigue		present but does not interfere with activity	interferes with activity	prevents daily activity
Generalized Rash		localized area of the skin (1 extremity only)	moderate area of the skin (2 or more body regions without whole body involvement)	most of the skin
Urticaria		localized area of the skin (1 extremity only)	moderate area of the skin (2 or more body regions without whole body involvement)	most of the skin

APPENDIX C: TOXICITY SCALES FOR LABORATORY ABNORMALITIES (SERUM CLINICAL CHEMISTRY)

Serum*,**	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)***
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

TOXICITY SCALES FOR LABORATORY ABNORMALITIES

** Laboratory values that fall in the normal range may be assigned a category of "Grade 0." *** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value. "ULN" is the upper limit of the normal range.

APPENDIX D:

(HEMATOLOGY)

Hematology*,*	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000

TOXICITY SCALES FOR LABORATORY ABNORMALITIES

Platelets Decreased cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000

*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

**Laboratory values that fall in the normal range may be assigned a category of "Grade 0."

APPENDIX E:

(URINE)

Urine*,**	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** Laboratory values that fall in the normal range may be assigned a category of "Grade 0."

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CLINICAL STUDY PROTOCOL AMENDMENT

Study Number: V132_01EXP

Protocol Title: A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine in Healthy Adults (18-45 years of age)

Amendment Number 1

Revised Protocol version 2.0 issued on 10 SEP 2014

The present amendment reflects changes to the Protocol version 1.0 issued on 30JUN14

DESCRIPTION OF CHANGE(S) AND RATIONALE:

CHANGE	LOCATION(S) OF CHANGE	RATIONALE FOR CHANGE
Interval for collection of solicited AE changed from collection until Day 15 to collection until Day 14 Allowed visit window for Visit 4 (Day 15) changed from -1/+1 to +1.	Synopsis, Times and Events Table 3, Section 3, Section 5, Section 7, Section 8	Diary Cards will be collected at Day 15. This change ensures that no incomplete Diary Cards will be presented at the Day 15 visit.
Chloride has been added to the Safety Laboratory Measurements.	Synopsis, Section 7	Correction of omission in Protocol version 1.0.
Maximum interval between Screening Visit and Day 1 changed from Day -21 to Day -28.	Times and Events Table 3, Section 3, Section 5	Allow more flexibility between Screening and Visit 1 (triggered by Christmas holiday period).
Time-points for frequent temperature assessments in the first 24h inpatient observation period have been specified.	Times and Events Table 3, Section 5	Ensure a potential transient temperature rise shortly after vaccination is captured.
Description of the stopping rules.	Section 3.6, Appendix A-E	Change is made to better reflect FDA standards.
Heart rate has been added to the vital sign measurements at Screening Visit and Visit 1.	Section 5	Correction of omission in Protocol version 1.0.
Description of medication errors or overdose.	Section 6.4	Change made to add new template text.
Corrections of typo's.	Throughout the document	Corrections of omissions in Protocol version 1.0.

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CLINICAL STUDY PROTOCOL V132_01EXP Version 2

A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine in Healthy Adults (18-45 years of age)

EUDRACT No. 2014-002430-31

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PROTOCOL SYNOPSIS V132_01EXP

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
Novartis Pharma Services AG	V132_01EXP	MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and Meningococcal C-CRM$_{197}$ Conjugate Vaccine
Title of Study: A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine in Healthy Adults (18-45 years of age)		
Study Period: Approximately 12 months for each subject		**Clinical Phase:** Phase 1

Background and Rationale:

Neisseria meningitidis (*N. meningitides*)serogroup C (MenC) is one of the major serogroups causing invasive meningococcal disease. Case fatality in Germany has ranged between 6% and 8% between 1999 and 2006, and has remained generally consistent across the different European countries, varying between 6-11%, with the case fatality rate being notably higher for serogroup C disease than for serogroup B. The safety and immunogenicity of the Novartis Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) has been confirmed through years of commercial use. For children over the age of 12 months, for adolescents and for adults a single dose is recommended. For infants between 2 and 12 months of age, the recommended schedule for primary immunization with the Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) is two doses given with an interval of at least 2 months (Novartis Meningococcal C-CRM$_{197}$ Conjugate Vaccine Investigator Brochure).

A more potent Meningococcal C-CRM$_{197}$ Conjugate Vaccine formulation might enable a reduction of the antigen dosage and/or a reduction in the number of doses needed in infants. One approach to achieve more potent well-characterized sub-unit vaccines - like the Novartis Meningococcal C-CRM$_{197}$ Conjugate Vaccine - is the use of new adjuvants that activate the Toll-like receptor (TLR) pathway.

Novartis is developing a small molecule immune potentiator (SMIP) LHD153 that is an agonist for TLR7. The objective driving the development of LHD153 is to achieve a vaccine adjuvant with strong immunopotentiating properties and minimal side effects. In line with this objective, it has been postulated that the ideal SMIP should remain local and target innate immune cells at the injection site. To this end, LHD153 contains a

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functional phosphonate group to allow for adsorption to aluminium hydroxide. The arginine salt derivative of this compound is LHD153R. Preclinical results from animal models for bacterial and viral antigens, including MenC, MenB, rabies, HIV and respiratory syncytial virus (RSV) showed increased functional antibodies and antigenspecific T-cells with LHD153R adsorbed to aluminium hydroxide (Aluminium Hydroxide/LHD153R) when compared to aluminium hydroxide adjuvanted controls. *In vitro* toxicity screens confirmed that LHD153R is not phototoxic, genotoxic or mutagenic. Furthermore, toxicology studies in dog and rats showed that intramuscular (IM) injection of Aluminium Hydroxide/LHD153R was well tolerated. Importantly, in contrast to free LHD153R, toxicokinetic analysis in rats and dogs confirmed very limited exposure of LHD153 when LHD153R was adsorbed to aluminium hydroxide after IM injection.

The aim of this Phase 1 clinical study is to assess the safety of Aluminium Hydroxide/LHD153R adjuvanted MenC-CRM_{197} conjugate vaccine (MenCCRM$_{197}$/Aluminium Hydroxide/LHD153R) and to compare the antibody-mediated immune response elicited by MenC-CRM_{197}/Aluminium Hydroxide/LHD153R with the licensed aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (Menjugate®). Furthermore, a comprehensive set of exploratory objectives has been selected to assess the systemic exposure of LHD153 after intramuscular injection of MenC-CRM_{197}/Aluminium Hydroxide/LHD153R, to evaluate the quality of the specific immune response against MenC-CRM_{197} in detail and to evaluate biomarkers that may be predictive of safety and/or innate immune activation.

The licensed Meningococcal C-CRM_{197} Conjugate Vaccine (Menjugate®) has been selected as the primary vaccine candidate to assess the safety and immunopotentiating properties of Aluminium Hydroxide/LHD153R for several reasons. Firstly, the safety and immunogenicity profiles of the Meningococcal C-CRM_{197} Conjugate Vaccine (Menjugate®) have been well established through years of commercial use. Secondly, a more potent MenC-CRM_{197} conjugate vaccine might enable a reduction of the antigen dosage or the number of doses needed in infants. Finally, the MenC-CRM_{197} conjugate is a well-characterized, single antigen preparation which provides an ideal setting to evaluate the potential of this new Aluminium Hydroxide/LHD153R adjuvant.

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Study Objectives:

Primary Safety Objective:

To assess the safety of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R as compared to that of aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine.

Primary Immunogenicity Objective:

To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine at Day 29, as measured by human complement serum bactericidal assay (hSBA) directed against MenC.

Secondary Immunogenicity Objectives:

1. To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal CCRM$_{197}$ Conjugate Vaccine, at Day 8 and Day 181 after vaccination, as measured by hSBA directed against MenC. Baseline antibody titers will also be measured by hSBA.
2. To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal CCRM$_{197}$ Conjugate Vaccine at Day 8, Day 29 and Day 181 after vaccination, as measured by an enzyme-linked immunosorbent assay (ELISA) to MenC. Baseline antibody concentrations will also be measured by ELISA.

Exploratory Objectives:

1. To evaluate the systemic exposure of LHD153 at several early time-points after IM injection of MenC-CRM197/Aluminium Hydroxide/LHD153R or aluminium hydroxide adjuvanted Meningococcal C-CRM197 Conjugate Vaccine.
2. To explore the frequency of B cells specific for MenC polysaccharide and CRM$_{197}$ protein at baseline (Day 1) and at Day 8, Day 29 and Day 181 after vaccination with

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MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R or the aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine. Subsequently, the B cell repertoire of the antigen specific B cells and the specific antibody functionality will be analyzed in a selected subset of subjects.

3. To explore the baseline T cell mediated immunity to CRM$_{197}$ and to evaluate the frequency and quality of CRM$_{197}$ specific T cells induced by MenC-CRM$_{197}$/Aluminium Hydroxide/ LHD153R compared to aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine at Day 8 and Day 29.
4. To evaluate biomarkers that may be predictive for safety and/or innate immune activation.

Study Design:

This Phase 1, randomized, observer-blind, dosage-escalation study will be performed at a single center. In total, approximately 80 healthy male and healthy non-pregnant female adults (18-45 years of age) will be enrolled in the study. Subjects will be randomized to receive a single IM vaccination of either the licensed aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine (i.e. 10 µg MenC conjugated to CRM$_{197}$, adjuvanted with 1 mg aluminium hydroxide) or one of four dosages of the investigational vaccine, MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R (i.e. 10 µg MenC conjugated to CRM$_{197,}$ adjuvanted with 1 mg aluminium hydroxide and one of four dosages [12.5, 25, 50 or 100 µg] of LHD153R).

For the dosage-escalation of LHD153R, the subjects will be enrolled into 1 of 4 cohorts, in a stepwise manner with 20 subjects per cohort. Subjects in all cohorts will be randomized in a 1:4 ratio, to receive either aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine (control) or MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R with increasing doses of LHD153R.Cohort 1 will receive 12.5 µg of LHD153R; Cohort 2 will receive 25 µg of LHD153R; Cohort 3 will receive 50 µg of LHD 153; and Cohort 4 will receive 100 µg of LHD153R (Table 1).

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Table 1. Subjects Randomized per Cohort and Treatment Dose Group

Cohort	Group	Subjects/ Group	MenC Dosage* (µg)	Adjuvant Dosages		Total Volume/Dose	Total Subjects/Group
				Aluminium Hydroxide (mg)	LHD153R (µg)		
1	A	4	10	1	0	0.5 mL	20
	B	16	10	1	12.5	0.5 mL	
2	A	4	10	1	0	0.5 mL	20
	C	16	10	1	25	0.5 mL	
3	A	4	10	1	0	0.5 mL	20
	D	16	10	1	50	0.5 mL	
4	A	4	10	1	0	0.5 mL	20
	E	16	10	1	100	0.5 mL	

*Conjugated to 12.5-25 µg CRM_{197}

After vaccination, all subjects will be confined to the clinical site for 24 hours for clinical observation, including but not limited to observations for solicited and unsolicited adverse events, body temperature measurements and blood sampling for exploratory endpoint measurements.

Importantly, all cohorts will have a staggered entry.

- For each cohort, the first 5 subjects (i.e. the first 1:4 randomization block) to receive either aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (n=1) or MenC-CRM_{197}/Aluminium Hydroxide/LHD153R (n=4) will be treated at a vaccination rate of 1 subject each day.
- After entry of the first 5 subjects in each cohort, the enrollment will be paused. The remaining 15 subjects for each cohort will be enrolled only after DMC review of the safety results obtained through Day 14 has been finalized (Table 2).
- Furthermore, after entry of all 20 subjects in each cohort, enrollment will be paused again. Enrollment of the first 5 subjects in the next cohort will only proceed after the Day 29 safety results of the previous cohort have been reviewed by the Data Monitoring Committee (DMC) (Table 2).

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Table 2. Overview of staggered entry of subjects for each cohort

Cohort	1st Stage of enrollment	MenC-CRM197/ Aluminium Hydroxide	MenC-CRM197/ Aluminium Hydroxide /LHD153R	2nd Stage of enrollment	MenC-CRM197/ Aluminium Hydroxide	MenC-CRM197/ Aluminium Hydroxide /LHD153R
1	First 5 subjects with vaccination rate of 1 subject/day	1	4	Remaining 15 subjects, after DMC review of Day 14 safety results	3	12
2		1	4		3	12
3		1	4		3	12
4		1	4		3	12

The DMC review after the first 5 subjects of each cohort and in between the cohorts will be performed according to predefined stopping/pausing guidelines used to ensure the safety of study subjects. These stopping/pausing guidelines are based on FDA guidance and with grading scales from the CBER Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials". See protocol section 3.6 for further details.

Safety Measurements

Schedule of safety data collection:

- Solicited local and systemic adverse events (AEs), body temperature and all unsolicited AEs will be collected until Day 14.
- All serious adverse events (SAEs), medically attended AEs, AEs leading to study withdrawal, new onset of chronic disease (NOCDs), and adverse events of special interest (AESIs) will be collected from the date of signed informed consent to study completion at Day 366.
- All concomitant medications administered in relation to the reported AEs will be collected from vaccination to study completion at Day 366.

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Solicited local AEs include injection site erythema, injection site induration, injection site pain and injection site swelling. Solicited systemic AEs include body temperature ≥ 38.0°C (as measured orally), loss of appetite, nausea, fatigue, generalized myalgia, generalized arthralgia, headache, chills, vomiting, diarrhea, generalized rash and urticaria.

All AESIs will be reported in the same manner as SAEs. All AEs will be monitored until resolution or, if the AE becomes chronic, a cause is identified. If an AE is unresolved at the conclusion of the study, a clinical assessment will be made by the investigator and the medical monitor to determine whether or not continued follow-up of the AE is warranted.

The relationship of the study treatment to any AE will be determined by the investigator as probably related, possibly related, or not related; the relationship of the study treatment to any SAE will be determined by the investigator as probably related/suspected, or not related.

Safety Laboratory Parameters

To assess laboratory AEs, blood and urine samples will be collected from each subject as outlined in Table 3 to perform blood chemistry, hematology, and urine analyses.

Safety laboratory samples will be drawn from all subjects at pre-vaccination screening (between Day -28 and Day -3) at Day 1 (pre-vaccination), at Day 8 and at Day 29. Safety laboratory assessments will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, liver function tests (ALT, AST), a complete blood count and C-reactive protein. A urine sample will be collected at the same time-points and will be assessed for the presence of protein, glucose and red blood cells.

Primary and Secondary Immunogenicity Measurements

Four blood samples per subject (i.e. at Day 1, Day 8, Day 29 and Day 181) will be collected for serum preparation and determination of antibody-mediated immune responses to MenC-CRM$_{197}$ as outlined in Table 3 and Table 4. See section 7.3 for further details.

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Exploratory Measurements

In all subjects who agree by signing a separate Informed Consent, additional blood samples will be collected at Day 1, Day 4, Day 8, Day 29 and Day 181 for exploratory assays as outlined in Table 3 and Table 4. The purpose of these assays is to assess the systemic exposure of LHD153, to determine the frequency and quality of B- and T-cells specific for MenC polysaccharide and/or CRM$_{197}$ and to evaluate biomarkers that may be predictive of safety and/or innate immune activation. Subsequently, MenC-CRM$_{197}$ specific B-cell repertoires as well as the MenC-CRM$_{197}$ specific antibody functionalities will be analyzed in a selected subset of subjects, dependent on the results from primary and secondary immunogenicity measurements and the volume of whole blood (specific B cell repertoire) and serum (specific antibody functionality) remaining for additional testing. See section 7.4 for further details. All exploratory analyses may be performed after the Clinical Study Report (CSR) has been completed, in which case these data will be submitted as an addendum to the CSR.

Number of Subjects planned:

Approximately 80 adult subjects will be randomized, with anticipated dropout rates of 5% by Day 181 (last serology time point), and 10%, by Day 366 (last safety time point).

Sample size is not driven by statistical assumptions for formal hypothesis testing, but the proposed number of subjects will be sufficient to provide a descriptive summary of the safety and immunogenicity of the study vaccine.

Study Population and Subject Characteristics:

Healthy adult male and female volunteers between 18-45 years of age, inclusive.

The list of inclusion and exclusion criteria is included in protocol section 4.0.

Study Vaccines:

The MenC-CRM$_{197}$ conjugate is a lyophilized powder consisting of 10 µg of MenC polysaccharide conjugated to 12.5-25 µg CRM$_{197}$ carrier protein. The MenC-CRM$_{197}$ lyophilized powder will be reconstituted with adjuvant by the unblinded designated site staff member who is to follow the procedure as described in the vaccine preparation

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instructions in the Investigator Site File (i.e. the vaccine will be prepared in the clinic prior to administration).

The lyophilized MenC-CRM$_{197}$ powder will be reconstituted with either:

(a) aluminium hydroxide adjuvant

(b) Aluminium Hydroxide/LHD153R adjuvant with specified dosages of LHD153R (12.5, 25, 50 or 100 µg)

The components for each formulation of MenC-CRM$_{197}$ will be provided in a separate kit.

Aluminium Hydroxide/LHD153R with specified dosages of LHD153R will be prepared by dilution of the highest Aluminium Hydroxide/LHD153R dosage (100 µg of LHD153R) with aluminium hydroxide.

In each cohort, subjects will be randomized to receive one injection of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R adjuvant or aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine. The 0.5 mL of vaccine will be injected IM in the deltoid muscle, with preference that the injection is administered in the nondominant arm.

Primary Safety Endpoint:
Safety will be assessed by measuring the frequency of local and systemic solicited AEs, unsolicited AEs, SAEs, AESIs, NOCDs, and safety laboratory data for all subjects. Specifically,

- The frequency and percentage of subjects with solicited local and systemic AEs through Day 14. Time intervals after vaccination that will be summarized are: 30 min post-vaccination, Days 1-4 (without 30 min), Days 5-8, Days 8-14, Days 1-8 (without 30 min) and Days 1-14 (without 30 min).
- The frequency and percentage of subjects with any unsolicited AEs from the day of vaccination (Day 1) to Day 14.
- The frequency and percentage of subjects with SAEs, medically attended AEs, AEs

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leading to study withdrawal, NOCDs, AESIs for the following time periods: day of signed informed consent until study completion (Day 366), day of vaccination (Day 1) to Day 29 and Day 29 to study completion (Day 366).

- The absolute values and changes in hematology, chemistry, and urinalysis parameters.
- The frequency and percentage of subjects with abnormal laboratory parameter values as classified by investigator normal ranges (low, normal, high) and as classified by CBER toxicity grading scales, when available.

Primary Immunogenicity Endpoint:

Geometric mean titers (GMTs) measured by hSBA directed against MenC from samples collected on Day 1 (baseline, before vaccination) and Day 29 as well as the GMR of the titers (Day 29 / Day 1).

Secondary Immunogenicity Endpoints:

- GMTs and corresponding GMRs measured by hSBA directed against MenC for samples collected at Day 8 and Day181.
- Percentage of subjects with hSBA seroresponse at Day 8, Day 29, and Day 181. seroresponse is defined as a post vaccination hSBA $\geq$8 for subjects with a baseline hSBA <4 or have an increase of at least 4 times the baseline hSBA level for subjects with pre-vaccination hSBA $\geq$4.
- Antibody geometric mean concentrations (GMCs) against MenC measured by ELISA for samples collected on Day 1 (baseline, prior to vaccination), Day 8, Day 29, and Day 181.
- The percentage of subjects with at least a 4-fold increase in antibody concentrations to MenC measured by ELISA on Day 8, Day 29, and Day 181 relative to baseline (Day 1).

Exploratory Endpoints:

Testing and analyses of exploratory endpoints may be performed after the Clinical Study Report (CSR) has been completed, in which case these data will be submitted as an

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addendum to the CSR.

1. Serum concentration of LHD153 at Day 1 baseline (prior to vaccination), Day 1 (1h , 2h, 4h, 8h, and 24h after vaccination) and Day 4 by LC-MS/MS.
2. Frequency of MenC polysaccharide-specific and CRM$_{197}$-specific B cells at Day 1 (baseline), Day 8, Day 29, and Day 181 by ELISPOT.
3. Diversity of the MenC polysaccharide-specific B-cell repertoire at Day 1 (baseline), Day 8, Day 29, and Day 181 by immunoglobulin cDNA sequencing.
4. Functionality of antigen specific antibodies will be assessed at Day 1 (baseline), Day 8, Day 29, and Day 181 by analysis of immunoglobulin isotype, glycosylation state and their ability to fix complement, to promote antibody-dependent cell mediated cytoxicity, to induce phagocytosis and to activate FcR+ cells. If the quantity of serum available for this specific exploratory objective is limited, assessments of immunoglobulin isotype, glycosylation state and complement fixing capacity will be prioritized over the other assessments.
5. Frequency and quality of T cells specific for CRM$_{197}$ at Day 1 (baseline), Day 8, and Day 29 by fluorescence activated cell sorting (FACS) analysis using intracellular staining with a panel of cytokines and surface markers to identify cell populations.
6. Serum concentrations of a panel of 30 chemokines and cytokines at Day 1 baseline (prior to vaccination), Day 1 (6h and 24h after vaccination), Day 4, and Day 8 by electrochemo-luminescence based assay.
7. Gene expression profile in whole blood at Day 1 baseline (prior to vaccination), Day 1 (6h and 24h after vaccination), Day 4, and Day 8 by RNA micro array analysis.

Statistical Analyses:

The study is exploratory in nature, thus analyses will be descriptive and no formal hypothesis testing will be performed.

Primary Safety Analyses

The primary safety analyses will be based on the safety set for solicited and unsolicited adverse events. There is no statistical null hypothesis associated with the safety

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objective, which will be analyzed descriptively.

Immunogenicity Analyses

The primary immunogenicity analyses will be based on the per-protocol set (PPS) on Day 29. The primary analyses will also be performed using the Full Analysis Set (FAS) as a measure of the sensitivity/robustness of the results. All other immunogenicity assessments will be performed using the PPS or the appropriate subset of subjects. The antibody concentrations/titers will be summarized using GMC/GMTs and two-sided 95% confidence intervals (CIs) constructed by exponentiation (base 10) of the least square means of the logarithmically transformed (base 10) antibody titer. The 95% CIs will be obtained from an analysis of covariance (ANCOVA) with baseline concentration/titer as a covariate. Additional details will be further described in the Statistical Analysis Plan.

The immunogenicity endpoints based on subjects meeting criteria for seroconversion or achieving a certain threshold value will be summarized using frequencies and percentages and associated two-sided 95% Clopper-Pearson CIs. For analyses of seroconversion, separate summaries may be provided based on seropositivity status at baseline.

Interim Analysis:

An Interim Analysis will be performed on the immunogenicity and safety data collected from all subjects until Day 29, after all cohorts have been enrolled. Further details regarding the interim analysis are contained in section 8.6.

Data Monitoring Committee:

A Data Monitoring Committee (DMC) will be implemented to review safety data during scheduled periodic reviews. The DMC will review safety data collected until Day 14, as described in the DMC charter and in the Statistical Analysis Plan, after enrollment of the first 5 subjects in each cohort, before proceeding with enrollment of the remaining subjects in each cohort. In addition, the DMC will review safety data collected until Day 29 after enrollment for each cohort. Enrollment of subjects in subsequent cohorts will only proceed after the DMC review is completed. The same enrollment sequence will be utilized for each cohort. Further information regarding the DMC is discussed in more detail in the protocol, section 3.7.

Table 3: Time and Events Table – Treatment Period (until Day 29)

	Visit Type	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit	Phone Call	Clinic Visit
	Study Day	**-28 to -3**	**1**	**4**	**8**	**15**	**22**	**29**
	Visit Window (Days)	**n/a**	**n/a**	**n/a**	**-1/+1**	**+1**	**n/a**	**-2/+2**
	Visit Number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**
Study Event	**References**							
Study Treatment								
Vaccination	Section 5.2		X					
Screening and Safety								
Informed Consent	Section 5.1.1	X						
Demographic Data & Medical History	Sections 5.1.2	X						
Physical Exam	Sections 5.1.2 and 5.2.1	X	X[a]					
Safety Laboratory blood draw (10 ml)	Section 7.1.7	X	X[a]		X			X
Urinalysis	Sections 7.1.7	X	X[a]		X			X
Pregnancy Test	Sections 5.1.2 and 5.2.1	X	X[a]					
Exclusion/Inclusion Criteria	Section 4.0	X	X[a]					
Randomization	Section 5.2.3		X[a]					
30 min and 24 hr Post Injection Assessment	Section 5.2.5		X[b]					
Subject Diary Dispensed with Training	Section 5.2.5		X					
Subject Diary Reminder	Section 5.2.5			X	X			

Subject Diary Reviewed and Collected	Section 5.3.1					X		
Assess all solicited AEs	Section 7.1.1 and 7.1.3					X		
Assess all unsolicited AEs	Sections 7.1.2 and 7.1.3	X	X	X	X	X		

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	Visit Type	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Phone Call**	**Clinic Visit**
	Study Day	**-28 to -3**	**1**	**4**	**8**	**15**	**22**	**29**
	Visit Window (Days)	**n/a**	**n/a**	**n/a**	**-1/+1**	**+1**	**n/a**	**-2/+2**
	Visit Number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**
Study Event	**References**							
Assess SAEs	Section 7.1.4	X	X	X	X	X	X	X
Assess AESIs	Section 7.1.4.1	X	X	X	X	X	X	X
Assess NOCDs, medically attended AEs, AEs leading to withdrawal	Sections 7.1.3	X	X	X	X	X	X	X
Assess relevant medications	Sections 5.1.2 and 6.5	X	X	X	X	X	X	X
Blood draws for Immunogenicity and Exploratory Objectives								
Serum Blood Draw (Primary and Secondary Objectives; 10 mL)	Section 3.5		X_a		X			X
Serum Blood Draw (Exploratory Objectives; 5 mL)	Section 3.5		X_c	X	X			
Whole Blood Draws (Exploratory Objectives; 2 mL)	Section 3.5		X_d	X				
Whole Blood Draw (Exploratory Objectives; 5 mL)	Section 3.5		X_e	X	X			

Whole Blood Draw (Exploratory Objectives; 50 mL)	Section 3.5		X_a		X			X

Notes:
a. Procedure must be performed prior to vaccination.
b. Body temperature measurement must be performed at 30 min, 2, 4, 6, 8, 10, 12, 20 and 24 hours after vaccination.
c. Three Serum Blood Draws (3 x 5ml) must be taken at Study Day 1, i.e. at baseline (prior to vaccination), at 6h and at 24h after vaccination.
d. Six whole Blood Draws (6 x 2 mL) must be taken at Study Day 1, i.e. at baseline (prior to vaccination) and at 1, 2, 4, 8 and 24h after vaccination.
e. Three Whole Blood Draw (3 x 5 mL) must be taken at Study Day 1, i.e. at baseline (prior to vaccination), at 6h and at 24h after vaccination

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Table 4: Time and Events Table – Follow-up Period (until Day 366)

	Visit Type	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Phone Call**	**Phone Call**	**Clinic Visit**
	Study Day	**85**	**113**	**181**	**209**	**271**	**366**
	Visit Window (Days)	**-7 to +7**	**-7 to +7**	**-7 to +7**	**-14 to +14**	**-14 to +14**	**-14 to +14**
	Visit Number	**7**	**8**	**9**	**10**	**11**	**12**
Study Event	**References**						
Safety							
Assess SAEs	Section 7.1.4	X	X	X	X	X	X
Assess AESI	Section 7.1.4.1	X	X	X	X	X	X
Assess NOCDs, medically attended AEs, AEs leading to withdrawal	Sections 7.1.3	X	X	X	X	X	X
Assess relevant medications	Sections 5.1.2 and 6.5	X	X	X	X	X	X
Blood draws for Immunogenicity and Exploratory Objectives							
Serum Blood Draw (Secondary Objective; 10 mL)	Section 3.5			X			

Whole Blood Draw (Exploratory Objectives; 50 mL)	Section 3.5			X			
Study Completion Procedures							
Study Termination[a]	Section 5.5						X

Notes:
a. Subjects who terminate the study early are recommended to complete certain study-related procedures. See section 5.5 for further details.

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LIST OF ABBREVIATIONS

ADCC	Antibody-dependent cell mediated cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BZN	Benzonaphthyridines
CBER	Center for Biologics Evaluation and Research
cDNA	Complementary deoxyribonucleic acid
CI	Confidence interval
CRF	Case report form
CRM_{197}	Cross Reacting Material 197
CSR	Clinical Study Report
DMC	Data Monitoring Committee
EC	Ethics committee
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
ELISPOT	Enzyme-Linked ImmunoSpot
EMA	European Medicines Agency
FACS	Fluorescence-activated cell sorting
FAS	Full analysis set
FDA	Federal Drug Agency
GCP	Good clinical practice
GMC	Geometric mean concentration
GMP	Good manufacturing practice

GMT	Geometric mean titer
GMR	Geometric mean ratio
HEENT	Head, ears, eyes, nose and throat
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
hSBA	Human complement serum bactericidal assay
ICF	Informed consent form
ICH	International Committee for Harmonization
IM	Intramuscular
IRB	Institutional review board
IV	Intravenous
LLQ	Lower limit of quantification
MenC	Meningococcal type C
MPL	Monophosphoryl lipid A
NCR	No carbon required
NOCD	New Onset of Chronic Disease
PEG	Polyethylene glycol
PO	Per oral
PP	Per protocol
RNA	Ribonucleic acid (RNA
SAE	Serious Adverse Event
SMIP	Small molecule immune potentiator
TLR	Toll-like receptor
VSAE	Vaccine serious adverse event

1.0 BACKGROUND AND RATIONALE

1.1 Background

MenC-CRM$_{197}$ Conjugate Vaccine

Meningococcal disease worldwide is predominantly a disease of infants and young children. *N. meningitidis* serogroup B and C remain the most prevalent strains in North America and Europe, (Rosenstein, N. et al., 2001) and together cause more than 95% of reported cases of meningococcal disease in Europe (Connolly, M, et al., 1999). In Europe, *N. meningitidis* serogroup C (MenC) is one of the major serogroups causing invasive disease. Case fatality in Germany has ranged between 6% and 8% between 1999 and 2006, and has remained generally consistent across the different European countries, varying between 6-11%, with the case fatality rate being notably higher for serogroup C disease than for serogroup B (European Centre for Disease Prevention and Control, 2011). Since MenC vaccination was added to Germany's routine schedule for children in 2006, there has been a reported decline in MenC incidence. However, the decline was not as rapid when compared to other European countries (Hellenbrand, W. et al., 2013).

The Novartis Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) comprises MenC oligosaccharides conjugated to the protein carrier, CRM$_{197}$, a nontoxic mutant of diphtheria toxin. The vaccine has been shown to be safe and immunogenic and able to prime infants, toddlers and young children for immunological memory (see Novartis Meningococcal C-CRM$_{197}$ Conjugate Vaccine Investigator's Brochure).

In Germany, the Standing Committee on Vaccination (STIKO) of the Robert Koch Institute recommends a single dose of MenC conjugate vaccine in children over the age of 12 months as part of the routine vaccination campaign (Robert Koch Institute Epidemiologisches Bulletin, August 2013). For specific indications, e.g. in case of postexposure prophylaxis, the recommended schedule for primary immunization of infants between 2 to 12 months of age with a MenC conjugate vaccine is two dosages given with an interval of at least 2 months.

Although the Novartis Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) represents an example of how vaccination with a well characterized, purified polysaccharide antigen can yield pivotal public health triumphs, there remains a need for further improvement of the MenC vaccine. A more potent MenC vaccine formulation might yield an increase in the magnitude of the antigen-specific immune response enabling a reduction of the antigen dosage. Furthermore, induction of a more rapid antigen-specific immune response may enable a reduction in the number of doses needed for post-exposure prophylaxis in infants.

Vaccine Adjuvants

Immunization with purified protein or polysaccharide antigens typically results in the induction of a modest antibody response with little or no T cell response when compared to vaccines comprised of whole or killed bacteria or viruses that have inherent immunepotentiating activity. The need to increase the immunogenic response of wellcharacterized and purified antigens that display suboptimal immunogenicity when used alone affirms the essential role for the use of adjuvants. Vaccine adjuvants may significantly reduce the amount of antigen needed (Del Giudice, G, et al., 2013) and may induce a more rapid immune response enabling a reduction in the number of doses in a regimen.

Besides reducing the antigen dosage or number of doses in the vaccine regimen, there is now an increased appreciation of the capacity of adjuvants to increase not just overall antibody titer but also to increase the number of functional antibodies and/or antibodies with higher affinity for vaccine antigens. Many pathogens, such as influenza viruses, HIV, human papilloma virus (HPV) and the malaria parasite, display substantial antigenic drift, subtype and/or strain variations. Therefore, the ability of adjuvants to broaden an immune response profile could be crucial to the success of vaccines against such targets. Previous studies have shown that the broadening effect of adjuvants may be mediated via expansion of B cell diversity, not merely through increased titers (Khurana, et al., 2010, 2011). Clinically, antibody response broadening by adjuvants such as AS04 or oil-inwater emulsions has been demonstrated in HPV vaccines and influenza, respectively (Bissett, SL et al., 2014; Del Giudice, G et al., 2013).

One unmet need is the development of vaccines for effective T cell responses. Several vaccines in development are aimed at eliciting T cell responses, which historically have not been induced by the most commonly used adjuvants in vaccines for human use, such as aluminium hydroxide. Therefore, an objective of many adjuvant discovery and development programs is to elicit more effective engagement of T-helper cells for optimizing the quality, breadth and durability of antibody responses, or, to induce effector CD4+ or CD8+ T cells to kill intracellular pathogens. One approach for new generation vaccines is the use of agonists for Toll-like receptors (TLRs) that activate innate immune receptors, mainly on antigen presenting cells, and facilitate the generation of T helper cell responses.

Adjuvants that are currently employed in human vaccines licensed for use in the USA and/or Europe include aluminium salts, oil-in-water emulsions (MF59, AS03 and AF03), virosomes, and AS04 (Alving, CR, et al., 2012). Among the most advanced adjuvants systems is AS04 which is used in the Cervarix® HPV vaccine and consist of the TLR4 ligand monophosphoryl lipid A (MPL) combined with aluminium salt. MPL, along with

QS21, is also part of the adjuvant system (AS01) in the RTS, S malaria vaccine from GlaxoSmithKline which has been evaluated in a Phase 3 clinical trial (Regules, JA, et al., 2011). Another clinically advanced adjuvant is CpG oligodeoxynucleotide (ODN), a TLR9 ligand contained in the Heplisav® vaccine candidate for hepatitis B from Dynavax, that has completed a Phase 3 clinical trial (Reed, SG, et al., 2013).

Small molecule immune potentiators as a new class of vaccine adjuvants

A new class of adjuvants, small molecule immune potentiators (SMIPs), has been identified that activate immune cells by targeting TLR7 and TLR8. Imiquimod and Resiquimod (R848) are clinically advanced TLR7 and/or TLR8 SMIPs that are used as immunotherapeutics. Although Imiquimod and Resiquimod have been studied extensively as vaccine adjuvants in preclinical models (Vasilakos et al. 2013), they were never optimized for this use and, in general, compare poorly to other pre-clinical and clinical adjuvant candidates. Furthermore, when Imiquimod is applied topically (it is a licensed topical treatment for viral and malignant skin lesions) it induces strong local and systemic inflammatory reactions, and is poorly tolerated (Bauza, et al. 2009; Campanelli, et al. 2005; Meyer, et al. 2008).

Unlike traditional drugs, TLR7 SMIPs activate innate immunity and initiate a cascade of immune responses that can have systemic impact and endure after the compound has been cleared from the organism. For SMIPs as vaccine adjuvants this difference is highlighted further by the fact that 2-3 local IM injections drive antigen-specific B and T cell responses at distal sites and these can provide protection in the form of immunologic memory (Tacken, et al. 2011; Ilyinskii, et al., 2014). Therefore, limiting the systemic exposure of the SMIP adjuvants has been postulated as an approach to both increase vaccine efficacy and minimize side effects associated with systemic and generalized inflammation. Novartis is currently developing a novel adjuvant, containing a SMIP from the benzonaphthryridines (BZN) series, LHD153, which targets TLR7. The objective driving the discovery of this new TLR7 ligand was to develop a vaccine adjuvant with high efficacy in increasing the vaccine specific immune response and with minimal side effects. To obtain this objective it was postulated that the ideal compound would remain localized at the site of injection to help trigger the immune reaction to vaccine antigens, yet maintain a low systemic distribution. At the same time this compound had to be soluble to make industrial scale-up and manufacturing feasible. Soluble BZN were engineered so that they could be formulated with aluminium salts with the aim of limiting their systemic exposure and keeping them localized in the muscle for short time after immunization. The strongest adsorption to aluminium hydroxide particles is obtained through ligand exchange of hydroxyl and/or phosphate groups on the surface of aluminium hydroxide or phosphate with soft anionic moieties such as phosphates, phosphonates, phosphites, sulfates and carboxylates. To drive the adsorption to

aluminium hydroxide through ligand exchange, LHD153 was functionalized with a polyethylene glycol (PEG) linker and a terminal phosphonate. Furthermore, LHD153 was stabilized with arginine salt to allow scale up for GMP manufacturing, yielding LHD153R. As predicted, unformulated LHD153R exhibited high levels of systemic exposure when injected IM in mice, rats and dogs, whereas the serum concentrations of LHD153R adsorbed to aluminium hydroxide (Aluminium Hydroxide/LHD153R) was dramatically reduced. Moreover, Aluminium Hydroxide/LHD153R remained localized to the injection site.

Preclinical studies using Aluminium Hydroxide/LHD153R to date confirm the activation of the TLR7 pathway and subsequent boost of both the humoral and cellular immune response. Moreover, Aluminium Hydroxide/LHD153R displays a unique pharmacokinetic profile as demonstrated by its minimal systemic exposure, potentially minimizing any systemic inflammatory response associated with tolerability issues. Aluminium hydroxide/LHD153R has achieved proof of concept in animal models using several vaccine antigens including MenC, MenB, rabies, HIV and respiratory syncytial virus (RSV). In vitro toxicity of LDH153R has been assessed, and in vivo nonclinical tolerability and safety of LHD153R and Aluminium Hydroxide/LHD153R have been evaluated in rats, dogs and non-human primates. LHD153R was not phototoxic, genotoxic or mutagenic (Ames and chromosomal aberration tests), and did not cause local or systemic toxicity in dogs or rats. Furthermore, Aluminium Hydroxide/LHD153R was well tolerated in rhesus monkeys.

1.2 Rationale

The aim of this study is to assess the safety of Aluminium Hydroxide/LHD153R adjuvanted MenC-CRM$_{197}$ conjugate vaccine (MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R) and to compare the antibody-mediated immune response elicited by MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R with the licensed aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®).

Furthermore, a comprehensive set of exploratory objectives has been selected to assess the systemic exposure of LHD153 after intramuscular injection and to evaluate the quality of the specific immune response against MenC-CRM$_{197}$ in detail and to evaluate biomarkers that may be predictive of safety and/or innate immune activation.

The licensed Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) has been chosen as the primary vaccine candidate to assess the safety and immunopotentiating properties of Aluminium Hydroxide/LHD153R for several reasons. Firstly, the safety and immunogenicity profiles of the Meningococcal C-CRM$_{197}$ Conjugate Vaccine have been well established through years of commercial use. Secondly, a more potent

Meningococcal C-CRM$_{197}$ Conjugate Vaccine might enable a reduction of the antigen dosage or the number of doses needed in infants between 2 and 12 months of age. Finally, the Meningococcal C-CRM$_{197}$ conjugate is a well-characterized, single antigen preparation which provides an ideal setting to explore the potential of this new Aluminium Hydroxide/LHD153R adjuvant.

2.0 OBJECTIVES

2.1 Primary Objectives

Primary Safety Objective

To assess the safety of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R as compared to that of aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine.

Primary Immunogenicity Objective

To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine at Day 29, as measured by human complement serum bactericidal assay (hSBA) directed against MenC.

2.2 Secondary Objectives

Secondary Immunogenicity Objective(s)

1. To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal CCRM$_{197}$ Conjugate Vaccine at Day 8 and Day 181 after vaccination, as measured by hSBA directed against MenC. Baseline antibody titers will also be measured by hSBA.
2. To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal CCRM$_{197}$ Conjugate Vaccine, at Day 8, Day 29 and Day 181 after vaccination, as measured by an enzyme-linked immunosorbent assay (ELISA) to MenC. Baseline antibody concentrations will also be measured by ELISA.

2.3 Exploratory Objectives

1. To evaluate the systemic exposure of LHD153 at several early time-points after IM injection of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R or Meningococcal CCRM$_{197}$ Conjugate Vaccine.
2. To explore the frequency of B cells specific for MenC polysaccharide and CRM$_{197}$ protein at baseline (Day 1) and at Day 8, Day 29 and Day 181 after vaccination with MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R or the aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine. Subsequently, the B cell repertoire of the antigen specific B cells and the specific antibody functionality will be analyzed in a selected subset of subjects.
3. To explore the baseline T cell mediated immunity to CRM$_{197}$ and to evaluate the frequency and quality of CRM$_{197}$ specific T cells induced by MenCCRM$_{197}$/Aluminium Hydroxide/ LHD153R compared to aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine at Day 8 and Day 29.
4. To evaluate biomarkers that may be predictive for safety and/or innate immune activation.

3.0 STUDY DESIGN

3.1 Overview of Study Design

This is a Phase 1, randomized, observer blind, adjuvant dosage-escalation study. It will be performed at a single center. In total, approximately 80 healthy male and healthy nonpregnant female adults (18-45 years of age) will be enrolled in the study.

Subjects will be randomized to receive a single IM vaccination of either the licensed aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) or the investigational vaccine, MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R.

The dosage of LHD153R will be escalated from 12.5 µg to 100 µg. For the dosageescalation of LHD153R, the subjects will be enrolled into 1 of 4 cohorts, in a stepwise manner with 20 subjects per cohort. Subjects in all cohorts will be randomized in a 1:4 ratio, to receive either aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine (control) or MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R with increasing doses of LHD153R.Subjects assigned to MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R in Cohort 1 will receive 12.5 µg of LHD153R; Subjects in Cohort 2 will receive 25 µg of LHD153R; Subjects in Cohort 3 will receive 50 µg of LHD153R; Subjects in Cohort 4 will receive 100 µg of LHD153R (Table 3.1-1).

Table 3.1-1: Subjects Randomized per Cohort and Treatment Dose Group

Cohort	Group	Subjects/ Group	MenC Dosage* (µg)	Adjuvant Dosages		Total Volume/Dose	Total Subjects/Group
				Aluminium Hydroxide (mg)	LHD153R (µg)		
1	A	4	10	1	0	0.5 mL	20
	B	16	10	1	12.5	0.5 mL	
2	A	4	10	1	0	0.5 mL	20
	C	16	10	1	25	0.5 mL	
3	A	4	10	1	0	0.5 mL	20
	D	16	10	1	50	0.5 mL	
4	A	4	10	1	0	0.5 mL	20
	E	16	10	1	100	0.5 mL	

*Conjugated to 12.5-25 µg CRM$_{197}$

All cohorts will have a staggered entry. For each cohort, the first 5 subjects (i.e. the first 1:4 randomization block) to receive either aluminium hydroxide adjuvanted

Meningococcal C-CRM$_{197}$ Conjugate Vaccine (n=1) or MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R (n=4) will be vaccinated at rate of 1 subject each day.

After entry of the first 5 subjects in each cohort, the enrollment will be paused. The remaining 15 subjects for each cohort will be enrolled only after DMC review of the safety results obtained through Day 14 has been finalized (Table 3.1-2). Furthermore, after entry of all 20 subjects in each cohort, enrollment will be paused again. Enrollment of the first 5 subjects in the next cohort will only proceed after the Day 29 safety results of the previous cohort have been reviewed by the DMC.

Table 3.1-2: Overview of staggered entry of subjects for each cohort

Cohort	1st Stage of enrollment	MenC-CRM$_{197}$/ Aluminium Hydroxide	MenC-CRM$_{197}$/ Aluminium Hydroxide /LHD153R	2nd Stage of enrollment	MenC-CRM$_{197}$/ Aluminium Hydroxide	MenC-CRM$_{197}$/ Aluminium Hydroxide /LHD153R
1	First 5 subjects with vaccination rate of 1 subject/day	1	4	Remaining 15 subjects, after DMC review of Day 14 safety results	3	12
2		1	4		3	12
3		1	4		3	12
4		1	4		3	12

Post-vaccination procedures include collection of urine specimens at Day 8 and Day 29 for safety assessment and blood specimens at Day 8, Day 29 and Day 181 for safety assessment and evaluation of the primary and secondary immunogenicity endpoints. Furthermore, additional blood specimens will be collected for assessment of exploratory endpoints at Day 1, Day 4, Day 8, Day 29 and Day 181 from those subjects that signed an additional informed consent concerning blood collection for exploratory assessment.

3.2 Study Period

Each subject should expect to participate in the study for approximately 12 months, from the time of enrolment through the last study visit.

3.3 Blinding Procedures

This study is designed as an observer-blind study. For each dosage cohort, subjects, investigators, laboratories and the sponsor will be blinded to vaccine assignments.

To maintain the blindness within each cohort, designated nurse(s) or physician(s) will be responsible for administering the study vaccines to the subjects, and will be instructed not to reveal the identity of the study vaccines neither to the subject nor to the investigative

site personnel (investigator, study nurse, monitor) involved in the conduct or monitoring of the trial. This (these) designated individual(s) will have no contact with the subjects after the administration of the study vaccine. Furthermore, unblinded monitors are assigned to reconcile actual vaccine treatment.

Study unblinding, at the group level, is planned for an Interim Analysis of the safety and immunogenicity data obtained up to Day 29 after all cohorts are enrolled and for full unblinding at the End of Study.

Except in the case of medical necessity, a subject's treatment should not be unblinded without the approval of the Sponsor. In such instance of medical emergency, every effort should be made to contact the Sponsor prior to unblinding. If unblinding should occur (by either accidental unblinding or emergency unblinding for a serious adverse event) prior to completion of the study, the investigator must promptly contact the Sponsor and document the circumstances on the appropriate forms. Instructions regarding emergency unblinding will be provided to the investigator.

3.4 Data Collection

3.4.1 Data Collected from Subjects

The following data will be collected from each subject over the duration of their study participation:

- Demographic Information
- Adverse Events
- Medical History
- Concomitant Medications
- Vital signs

All data collected must only be identified using the Subject ID, as described in section 5.2.3.

3.4.2 Tools Used for Data Collection

Data will be recorded in the Subject Diary and collected on Case Report Forms (CRFs).

Subject Diary

Subject Diaries will be the only source document allowed for solicited local and systemic adverse events (including body temperature measurements), starting after the initial 24 hours post-vaccination observation period at the clinic. The following additional rules apply to documentation of safety information collected in the Subject Diary:

1. No corrections or additions to the Subject Diary will be allowed after it is delivered to the site.
2. Any blank or illegible fields on the Subject Diary must be described as missing in the CRF.
3. Any corrections to the Subject Diary must be performed by the person completing the Subject Diary and should include a single strike through line through the incorrect value or text with a brief explanation for each change, the initials of that person, and date of correction.

Case Report Forms

This study utilizes CRFs to collect study-related data from each subject. A qualified site staff member(s) is required to enter subject data in the CRFs in English based on the medical information available in each subject's record. The following additional rules apply to documentation of Subject Diary information collected in the CRFs:

1. The site must enter all readable entries in the Subject Diary into the CRF, including those values that may be biologically implausible (e.g. body temperature: 400°C).
2. Any illegible or implausible data should be reviewed with the subject. If an underlying solicited or unsolicited adverse event is described on review with the subject, this should be described in the source document and reported as an unsolicited adverse event in the appropriate CRF (e.g., if the subject above confirms body temperature of 40°C on the day in which body temperature: 400°C was written into his/her Subject Diary, this fever of 40°C should be recorded in the appropriate CRF).
3. Any newly described safety information (including a solicited adverse event) must not be written into the Subject Diary and must be described in the study file as a verbally reported adverse event. Any adverse event reported in this fashion must be described as an unsolicited adverse event and therefore, entered in the appropriate CRF.

Data should be entered into the CRF in a timely fashion following each subject's clinic visit, study procedure, or phone call. Each subject's CRF casebook will be compared with the subject's source records by a Novartis-approved study monitor (or designee) over the duration of the study in order to ensure data collection accuracy.

3.5 Collection of Clinical Specimens

The following clinical specimens are required to be collected from each subject in this study:

- Blood
- Urine

Processing of each specimen should be completed by a qualified site member. Testing of clinical specimens will be performed by a Novartis or designated laboratory.

Blood Specimens

Before Vaccination

- At the Pre-vaccination Screening Visit (between Day -28 to -3) one sample of approximately 10 ml blood will be drawn from all subjects.
- At Visit 1 (Day 1) - prior to vaccination – two samples of approximately 10 ml blood will be drawn from all subjects.
- At Visit 1 (Day 1) - prior to vaccination - the following blood samples will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays:
  - One sample of approximately 2 ml
  - Two samples of approximately 5 ml
  - One sample of approximately 50 ml

After Vaccination

- At Visit 1 (Day 1) - 1 hour after vaccination - one sample of approximately 2 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 2 hours after vaccination - one sample of approximately 2 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 4 hours after vaccination - one sample of approximately 2 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.

- At Visit 1 (Day 1) - 6 hours after vaccination – two samples of approximately 5 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 8 hours after vaccination - one sample of approximately 2 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 24 hours after vaccination - the following blood samples will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays:
  - One sample of approximately 2 ml
  - Two samples of approximately 5 ml
- At Visit 2 (Day 4) the following blood samples will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays:
  - One sample of approximately 2 ml
  - Two samples of approximately 5 ml
- At Visit 3 (Day 8) two samples of approximately 10 ml blood will be drawn from all subjects.
- At Visit 3 (Day 8) the following blood samples will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays
  - Two samples of approximately 5 ml
  - One sample of approximately 50 ml
- At Visit 6 (Day 29) two samples of approximately 10 ml blood will be drawn from all subjects.
- At Visit 6 (Day 29) one sample of approximately 50 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 9 (Day 181) one sample of approximately 10 ml blood will be drawn from all subjects.
- At Visit 9 (Day 181) one sample of approximately 50 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.

The blood will be used for screening and safety laboratory assessments, immunological serology assays, pharmacokinetic analysis, cell mediated immunity assays and gene expression and protein production assays. See section 5.1.2, section 5.2.1 and section 7.0 for additional details.

Processing of each blood specimen should be completed in accordance with the study specific Clinical Specimen Laboratory Manual.

The total amount of blood collected over the study period for all subjects will be approximately 80 ml.

For subjects that signed an additional informed consent for blood collection for exploratory assays the total amount of blood collected over the study period will be approximately 344 ml.

Urine Specimens

Urine will be collected at the Pre-vaccination Screening Visit (between Day -28- to -3), at Visit 1 (Day 1; before vaccination), at Visit 3 (Day 8) and at Visit 6 (Day 29). Results will be recorded in the source document and CRF.

Urine will be collected from all subjects for safety laboratory assessments and drugs-ofabuse testing. Furthermore, urine will be collected for pregnancy testing in all females.

3.6 Stopping/Pausing Guidelines

Stopping/pausing guidelines are predefined criteria that halt the conduct of a study (either a vaccine group or the entire study). These guidelines are used to ensure the safety of study subjects.

The following criteria, based on FDA guidance and with grading scales adapted from the CBER Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive vaccine Clinical Trials", will be used for this study:

1. The study will be halted (no new enrollments and no further investigational product administered until a full safety review by the DMC and consultation with the IRB/EC and the health authorities is completed) if one of the following occurs
    a. One subject experiences a serious adverse event (SAE) assessed as possibly or probably related to investigational product or,

b. There is a subject death assessed as possibly or probably related to the investigational product.

2. If one or more subjects experience a Grade 4 AE (see Appendix C, D, and E), vital sign or laboratory abnormality that cannot be clearly attributed to another cause, vaccination will be suspended until a full safety review by the DMC is performed.
3. If six or more subjects experience a Grade 3 AE (see Appendix A, B, C, D, and E), vital sign or laboratory abnormality, dosage escalation will be suspended for that vaccine until a full safety review by the DMC is performed.

The sponsor or the investigator (following consultation with the sponsor) has the right to discontinue the study at any time. If the clinical study is prematurely terminated, the investigator must promptly inform the study subjects and must assure appropriate therapy and follow-up for the subjects. All procedures and requirements pertaining to the archiving of the documents must be followed. All other study materials (such as study vaccines) must be returned to the sponsor or destroyed after sponsor approval.

3.7 Data Monitoring Committee

A DMC will be formed to review safety data during scheduled periodic reviews. The DMC may also perform reviews on an ad hoc basis as needed. DMC membership will consist of at least 3 individuals who are external to the site and sponsor, and will include 1 statistician who is independent from the study team.

Subjects will be enrolled in a stepwise manner in each of the four vaccine dosage cohorts (Cohort 1: 12.5 µg LHD153R, Cohort 2: 25 µg of LHD153R, Cohort 3: 50 µg of LHD153R and Cohort 4: 100 µg of LHD153R). The DMC will review all safety data, as described in the DMC charter and in the Statistical Analysis Plan, after the first 5 subjects in each cohort have completed Visit 4 and their data are available for analysis, and before enrollment of the remaining subjects in each cohort. In addition, the DMC will review all safety data after enrollment in each cohort has been completed, after Visit 6 and their data are available for analysis/review and before proceeding with enrollment of the subsequent cohort.

The specific roles and responsibilities of the DMC members and other personnel involved will be documented in the DMC charter. The DMC charter will be finalized before the start of the study and will outline in detail all pausing and stopping rules according to the Clinical Study Protocol.

3.8 Premature Withdrawal from Study

Subjects may withdraw at any time, or be dropped from the study at the discretion of the investigator should any untoward effects occur and/or for safety reasons. In addition, a subject may be withdrawn by the investigator or the Sponsor if he/she violates the study plan or for administrative reasons. The investigator or study coordinator must notify the Sponsor immediately when a subject has been withdrawn due to an adverse event.

The circumstances above are referred to as premature withdrawal from the study, and the reason for premature withdrawal should be clearly documented and detailed in the source documentation. The investigator should make every attempt to evaluate the subject's safety, including resolution of ongoing AEs, at the time of premature withdrawal. If a subject wants to withdraw from the study prior to the last planned study visit, the subject will be asked to be followed for safety for the duration of the study. When a subject withdraws, or is withdrawn, from the study, the procedures described in section 5.5.1 should be completed if possible.

The reasons for premature withdrawal from the study include: Adverse event, death, withdrawal of consent, lost to follow-up, administrative reason, and protocol deviation. These reasons are described in greater detail below.

Adverse Event

For any subject withdrawn from study participation prior to the planned Study Termination Visit, it is important to determine if an AE was associated with the reason for discontinuing the study. This AE must be identified on the appropriate CRF page by indicating "Withdrawn from study due to AE". Any ongoing AEs at the time of study withdrawal must be followed until resolution or stabilization.

Death

For any subject withdrawn from study participation due to death, this should be noted on the appropriate CRF page and the associated SAE that led to the death must be reported.

Withdrawal of consent

The subject can withdraw consent for participation in the study at any time without penalty or loss of benefit to which the subject is otherwise entitled. Reason for early termination should be deemed as "withdrawal of consent" if the subject withdraws from participation due to a non-medical reason (i.e., reason other than AE). If the subject intends to withdraw consent from the study, the investigator should clarify if the subject will withdraw completely from the study or if the subject will continue study participation for safety, or a subset of other study procedures. If the subject requests complete

withdrawal from the study, no further study interventions will be performed with the subject.

Lost to Follow-Up

For subjects who fail to show up for study visits (clinic or telephone contacts), study staff is encouraged to make at least three documented attempts to contact the subject by telephone and at least one documented written attempt to contact the subject to encourage the completion of study termination procedures. These efforts to contact the subject must be recorded in the source document. The termination date for the subject to be captured on the appropriate CRF page is the date of the last contact (clinic visit or telephone) with the subject.

Administrative Reason

Examples for subjects withdrawn from the study due to administrative reason can include: Sponsor decision to terminate the study, subject meeting a pre-specified withdrawal criterion, subject discontinuation for insurance issues, moving, no time, etc. This reason should be noted in the appropriate CRF page and any ongoing AEs at the time of study withdrawal must be followed until resolution/stabilization.

If the clinical study is prematurely terminated by the Sponsor, the investigator is to promptly inform the study subjects and local EC/IRB and should assure appropriate therapy and follow up for the subjects. All procedures and requirements pertaining to the archiving of study documents should be followed. All other study materials (study medication/vaccines, etc.) must be returned to the Sponsor.

For subjects who are withdrawn from the study due to receipt of an excluded medication/vaccination or due to significant protocol non-compliance, this reason should be noted in the appropriate CRF page.

Protocol Deviation

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. In general, subjects associated with protocol deviations may remain in the study unless continuation in the study jeopardizes the subject's health, safety, or rights.

Investigators will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are

permitted. If the investigator feels a change to the protocol would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/EC and health authorities it cannot be implemented.

Any subject who becomes pregnant during the study should be encouraged to continue participating in the study for safety follow-up. The site must complete a Pregnancy Report CRF (initial report) as soon as possible after learning of pregnancy occurrence (see section 7.1.6 for further details). If the subject withdraws from the study for any of the above categories except death, the site will obtain permission from the subject to continue to remain in contact with her until the outcome of the pregnancy is known, even if the outcome is not known until after the subject reaches the end of the routine study period.

3.9 End of Study

Most clinical trials intended to support the efficacy/immunogenicity and safety of an Investigational Product proceed to full completion of planned sample size accrual.

A subject is considered to have completed this study when he/she has: (1) received the intended dose of study vaccine and (2) completed 365 days (Visit 12) of safety follow-up after receiving the study vaccine.

Evaluation of the primary and secondary immunogenicity objectives requires the testing of biological samples from all study subjects, which can only be completed after all samples are collected. The last samples for the analysis of the primary and/or secondary objectives will be taken at Visit 9 (Day 181). For the purpose of this protocol, End of Study is defined as the completion of the testing of such biological samples, to be achieved no later than 8 months after collection of the last biological sample at Visit 9.

4.0 SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

In order to participate in this study, all subjects must meet all of the inclusion criteria described.

1. Male or female individuals of 18 through 45 years of age on the day of informed consent.
2. Healthy volunteers with good physical and mental health status, determined on the basis of the medical history, a physical examination and the results of the screening tests as judged by the investigator.
3. Individuals who have voluntarily given written informed consent after the nature of the study has been explained according to local regulatory requirements, prior to study entry.
4. Individuals who can comply with study procedures including follow-up[1].
5. Individuals that are able to understand, read and write German language.
6. Females of childbearing potential who are using an effective birth control method[2] which they intend to use for at least 30 days after the study vaccination.

4.2 Exclusion Criteria

Each subject must not have or must not be:

1. Progressive, unstable or uncontrolled clinical conditions.
2. Hypersensitivity, including allergy, to any component of vaccines, medicinal products or medical equipment whose use is foreseen in this study.

[1] A subject is considered to be compliant if the Investigator judges that the subject will complete the Subject Diary, return for all the follow-up visits and be available for telephone calls as scheduled in the study.

[2] The following birth control methods are considered effective:

- Hormonal contraceptive (such as oral, injection, transdermal patch, implant) if used for at least 30 days prior to informed consent
- Diaphragm with spermicide, tubal occlusion device
- Intrauterine device (IUD)

- Tubal ligation
- Male partner using condom with spermicide
- Male partner having been vasectomized at least six months prior to informed consent

3. Clinical conditions representing a contraindication to intramuscular vaccination and blood draws.
4. Abnormal function of the immune system resulting from:
   a. Clinical conditions.
   b. Systemic administration of corticosteroids (PO/IV/IM) for more than 14 consecutive days within 90 days prior to informed consent.
   c. Administration of antineoplastic and prescription immunomodulating agents or radiotherapy within 90 days prior to informed consent.
5. Received immunoglobulins or any blood products within 180 days prior to informed consent.
6. Received an investigational or non-registered medicinal product within 30 days prior to informed consent or intend to participate in another clinical study at any time during the conduct of this study.
7. Vulnerable subjects (e.g. persons kept in detention), study personnel or an immediate family or household member of study personnel, subjects with legal incapacity or limited legal capacity
8. Any relevant deviation from the laboratory parameters at screening as judged by the investigator.
9. Previously received any vaccine that included a MenC antigen.
10. Previously suspected or confirmed disease caused by *N. meningitides.*
11. Had household contact with and/or intimate exposure to an individual with culture proven MenC.
12. A positive serum or urine pregnancy test prior to the study vaccine administration or are currently lactating.
13. A positive drugs-of-abuse test prior to the study vaccine administration
14. Received any other vaccines within 30 days prior to enrolment in this study or who are planning to receive any vaccine within 30 days from the administration of study vaccines.

15. Any other condition that, in the opinion of the investigator, might interfere with the results of the study or pose additional risk to the subject due to participation in the study.

4.3 Criteria for Delay of Vaccination or Blood Draw

There may be instances when individuals meet all eligibility criteria for vaccination or blood draw yet have a transient clinical circumstance which may warrant delay of vaccination or blood draw. Under such circumstances, a subject may be considered eligible for study enrolment after the appropriate window for delay has passed and inclusion/exclusion criteria have been rechecked, and if the subject is confirmed to be eligible.

Reasons for delay of vaccination include:

- Body temperature elevation ≥38.0°C (measured orally) within 3 days prior to intended study vaccination.
- Use of antipyretics and/or analgesic medications within 24 hours prior to vaccination.

Reasons for delay of blood draw include:

- Subject has received a dose of systemic antibiotics less than 6 days before blood collection for the hSBA directed against MenC.

5.0 STUDY PROCEDURES

The sections that follow provide an overview of the procedures that are to be followed in enrolling, evaluating, and following subjects who participate in this clinical study. Visits can be either clinic visits or safety follow-up telephone calls, as specified in the Table below and in the Time and Events Tables 3 and 4 of the Study Synopsis.

Table 5.0-1: Study procedures

Visit Category	Procedures
Pre-vaccination Clinic Visit	Section 5.1 describes procedures to be followed prior to subject enrollment, including: informed consent and screening procedures.
Vaccination Clinic Visit	Section 5.2 describes procedures to be followed during the vaccination clinic visit, including: prevaccination procedures, enrolment, randomization, vaccination and post-vaccination procedures.
Post-vaccination Visits	Section 5.3 describes follow-up clinic visits and safety follow-up calls.
Unscheduled Visits	Section 5.4 describes possible procedures to be followed at unscheduled clinic visit.
Study Termination Visit	Section 5.5 describes procedures to be followed at the last study visit for a subject (may include early termination visit).

5.1 Pre-vaccination Clinic Visit(s)

The Pre-vaccination Clinic Visit must be performed in the period between Day -28 and Day -3.

This section describes the procedures that must be performed for each potential subject prior to enrollment, including obtaining informed consent and screening.

5.1.1 Informed Consent

"Informed consent" is the voluntary agreement of an individual or his/her legal guardian(s) to participate in research. Consent must be given with free will of choice, and without undue inducement. The individual must have sufficient knowledge and understanding of the nature of the proposed research, the anticipated risks and potential benefits, and the requirements of the research to be able to make an informed decision.

Informed consent following local IRB/EC guidance **must** be obtained before conducting any study-specific procedure (i.e., all of the procedures described in the protocol). Prior to any additional blood sample collection for exploratory objectives, a secondary informed consent **must** be signed by subjects. The process of obtaining informed consent should be documented in the subject source document in addition to maintaining a copy of the signed and dated informed consent.

5.1.2 Screening

After an individual has consented to participate in the study and informed consent is signed, that individual will be given a unique Screening Number. The subject's unique Screening Number will be documented in the Screening and Enrolment log. The eligibility of the subject will be determined based on the inclusion and exclusion criteria listed in section 4.0 and evaluated during this screening procedure.

Screening procedures at the Pre-vaccination Clinical Visit (between Day -28 and Day -3) will include the following:

- Review of demographic data, including age, gender, race, body weight and height.
- Review of medical history, including but not limited to any medical history, ongoing illnesses or injuries that may be relevant to subject eligibility for study participation. Relevant medical history can also include any medical history that contributes to the understanding of an adverse event that occurs during study participation, if it represents an exacerbation of an underlying disease/pre-existing problem.
- Perform physical examination, including but not limited to:
  - Assessment of general appearance
  - Collection of vital signs, including body temperature, blood pressure, heart rate and respiratory rate
  - Examination of head, ears, eyes, nose and throat (HEENT)
  - Examination of skin
  - Auscultation of heart and lungs
- Collection and review of prior and concomitant medications or vaccinations taken prior to start of study (refer to section 6.5 for further details).
- Collection of any unsolicited AEs occurring prior to administration of the study vaccine.

- Blood draw (approximately 10 ml) for Safety Laboratory assessments, measurement of Hepatitis B surface antigen, anti-Hepatitis C virus antibodies, anti-HIV 1 and 2 antibodies and serum pregnancy test (all women).
- Urine sample for Safety Laboratory assessments and drugs-of-abuse testing.

NOTE: A general physical examination is to be performed by a qualified health care practitioner. "Qualified health care practitioner" refers to any licensed health care professional who is permitted by institutional policy to perform physical examinations and who is identified within the Study Staff Signature Log.

Data collected during the Pre-vaccination Screening Clinic Visit must be written in the source document (see section 9.1) and will be captured in the screening CRF Forms. In the event that the individual is determined ineligible for study participation, he/she is considered a screen failure. The reason for screen failure must be documented in the Screening and Enrolment log.

5.2 Vaccination Clinic Visit(s)

This section describes the procedures to be performed at the Vaccination Clinic Visit (Visit 1, Day 1), including: pre-vaccination procedures, enrolment, randomization, prevaccination blood draw, vaccination and post-vaccination procedures.

5.2.1 Pre-vaccination Procedures

During pre-vaccination procedures at Visit 1 (Day 1), the eligibility of the subject will be confirmed based on the inclusion and exclusion criteria listed in section 4.0.

Pre-vaccination procedures at Visit 1 (Day 1) will include the following:

- Review of systems by means of a structured interview that queries the subject as to any complaints the subject has experienced across each organ system.
- Perform physical examination, including but not limited to:
  - Assessment of general appearance
  - Assessment of body weight and collection of vital signs, including body temperature, blood pressure, heart rate, and respiratory rate
  - Examination of head, ears, eyes, nose and throat (HEENT)
  - Examination of skin

- Auscultation of heart and lungs

- Collection and review of prior and concomitant medications or vaccinations taken, or recalled, since the last visit (refer to section 6.5 for further details).
- Collection of any unsolicited AEs occurring prior to administration of the study vaccine.
- One blood sample (approximately 10 ml) will be drawn from all subjects for serology testing.
- One blood sample (approximately 10 ml) will be drawn from all subjects for baseline Safety Laboratory assessments.
- Urine sample for baseline Safety Laboratory assessments, pregnancy testing (all women) and drugs-of-abuse testing.
- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and volume of blood draws are provided in section 3.5.

NOTE: A general physical examination is to be performed by a qualified health care practitioner. “Qualified health care practitioner” refers to any licensed health care professional who is permitted by institutional policy to perform physical examinations and who is identified within the Study Staff Signature Log.

Data collected during pre-vaccination procedures at Visit 1 must be written in the source document (see section 9.1). In the event that the individual is determined ineligible for study participation, he/she is considered a screen failure. The reason for screen failure must be documented in the Screening and Enrolment log. If the individual is determined to be eligible for the study, he/she can be enrolled into the study.

5.2.2 Enrolment

After an individual is determined to be eligible for study participation, the investigator will enroll the subject into the Electronic Data Capture (EDC) system where the randomization to the treatment group will occur. The Screening Number ceases to be used and remains in the Screening and Enrolment Log only.

If for any reason, after signing the informed consent form (ICF), the subject who is eligible and enrolled fails to be randomized, this is called a randomization failure. In this case the early termination study procedures must be applied. The reason for all randomization failures should be recorded in the Screening and Enrolment Log and in the

source document as specified in the Source Data Agreement. The information on subjects who are randomization failures should be kept distinct from subjects who are screen failures, as described in section 5.1.2 and section 5.2.1.

5.2.3 Randomization

Enrolled subjects will be randomized and automatically assigned a unique Subject ID. The Subject ID will be the subject's unique identification number for all CRFs and associated study documentation that will be used for the duration of the study.

If for any reason, after signing the informed consent form (ICF), the eligible subject is enrolled and randomized but fails to undergo treatment, this is an Early Termination and the reason should be recorded in source document as specified in the Source Data Agreement/Source Data Verification Form. The information on these Early Termination subjects should be kept distinct in the source documentation from randomization failures, which are described in section 5.2.2.

5.2.4 Vaccination

After completing the pre-vaccination procedures at Visit 1 (Day 1), administer the vaccine to the subject according to the procedures described in section 6.3. Observe the blinding procedures described in section 3.3.

5.2.5 Post-vaccination Procedures

The following post-vaccination procedures will be performed at Visit 1 (Day 1):

- After vaccination, the subject will be observed for at least 30 minutes for any immediate solicited and unsolicited AEs and a body temperature measurement at 30 min after vaccination. All safety and body temperature data collected during this time are to be recorded in the subject's source document.
- After vaccination, the subject will be observed for at least 24 hours at the clinic including observation for solicited and unsolicited AEs and body temperature measurements . Body temperature measurements must be performed at 2, 4, 6, 8, 10, 12, 20 and 24 hours after vaccination. All safety and body temperature data collected during this time are to be recorded in the subject's source..
- From those subjects that signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn in the first 24 hours after vaccination. Details regarding the number and volume of post-vaccination blood draws are provided in section 3.5.

After the initial 24 hours inpatient observation period, a Subject Diary will be used in this study to document solicited and unsolicited AEs until Day 14. The Subject Diary is the only source for collection of solicited AEs after the initial 24 hours inpatient observation period. Therefore, it is critical that the subject completes the Subject Diary correctly.

The following training regarding completion of the Subject Diary must be provided:

- The subject should be trained on how and when to complete each field of the Subject Diary.
- The subject should be trained on how to self-measure local solicited adverse events and body temperature. The measurement of solicited local adverse events is to be performed using the ruler provided by the site.
- The subject should be instructed how to perform body temperature measurement using the thermometer provided by the site. If the subject feels unusually hot or cold during the day, the subject should check their body temperature. If the subject has fever, the highest body temperature observed that day should be recorded in the Subject Diary.

Subject Diary training should be directed at the individual(s) who will perform the measurements of adverse events and who will enter the information into the Subject Diary. This individual may not be the subject, but if a person other than the subject enters information into the Subject Diary, this person's identity must be documented in the Subject Diary. Any individual that writes in the Subject Diary must receive training on completion of the Diary Card at the time of the visit. This training must be documented in the subject's source record.

The site should schedule the next study activity (clinic visit) with the subject.

The subject will receive a written reminder of the next planned study activity. The subject will be reminded to complete the Subject Diary and to contact the site if there are any questions, and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

5.3 Post-vaccination Visit(s)

5.3.1 Subject Diary Reminder, Safety Follow-up and/or Post-vaccination Blood Draw Clinic Visits

Subject Diary reminder, Safety follow-up and/or post-vaccination blood draw clinic visits will be performed on Day 4 (Visit 2), Day 8 (Visit 3), Day 15 (Visit 4), Day 29 (Visit 6), Day 85 (Visit 7), Day 113 (Visit 8) and Day 181 (Visit 9)

At Day 4 (Visit 2) the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. All unsolicited AEs, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. Any concomitant medications or vaccinations associated with those events must also be recorded on the source documents.
- All subjects will be reminded to complete the Subject Diary and to contact the site if there are any questions, and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit. No changes to the Subject Diary should be done at the clinic visit.
- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and volume of blood draws are provided in section 3.5.
- The site should schedule the next study activity (clinic visit) with the subject and the subject will receive a written reminder of the next planned study activity.

At Day 8 (Visit 3) the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. All unsolicited AEs, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. Any concomitant medications or vaccinations associated with those events must also be recorded on the source documents.
- The subject will be reminded to complete the Subject Diary and to contact the site if there are any questions, and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to hospitalization

or an emergency room visit. No changes to the Subject Diary should be done at the clinic visit. Blood draw (approximately 10 ml) from all subjects for Safety Laboratory assessments.

- Urine sample from all subjects for Safety Laboratory assessments.
- Blood draw (approximately 10 ml) from all subjects for serology testing.
- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and volume of blood draws are provided in section 3.5.
- The site should schedule the next study activity (clinic visit) with the subject and the subject will receive a written reminder of the next planned study activity.

At Day 15 (Visit 4) the following procedures will be performed:

- The Subject Diary will be collected and reviewed. No changes to the Subject Diary should be done at the clinic visit. For details on the Subject Diary see sections 3.4.2, and 5.2.5. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. All unsolicited AEs until Day 14, solicited local and systemic AEs persisting at Day 14, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. All concomitant medications or vaccinations associated with those events must also be recorded on the source documents.
- The site should schedule the next study activity (safety phone call) with the subject.
- The subject will receive a written reminder of the next planned study activity. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

At Day 29 (Visit 6) the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. Any solicited local and systemic AEs continuing beyond Day 14, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. All concomitant

medications or vaccinations associated with those events must also be recorded on the source documents.

- Blood draw (approximately 10 ml) from all subjects for Safety Laboratory assessments.
- Urine sample from all subjects for Safety Laboratory assessments.
- Blood draw (approximately 10 ml) from all subjects for serology testing.
- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and volume of post-vaccination blood draws are provided in section 3.5.
- The site should schedule the next study activity (clinic visit) with the subject.
- The subject will receive a written reminder of the next planned study activity. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

At Day 85 and Day 113 (Visit 7 and Visit 8), the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. Any solicited local and systemic AEs continuing beyond Day 14, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. All concomitant medications or vaccinations associated with those events must also be recorded on the source documents.
- The site should schedule the next study activity (clinic visit) with the subject.
- The subject will receive a written reminder of the next planned study activity. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

At Day 181 (Visit 9), the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since

the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. Any solicited local and systemic AEs continuing beyond Day 14, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. All concomitant medications or vaccinations associated with those events must also be recorded on the source documents.

- Blood draw (approximately 10 ml) from all subjects for serology testing.
- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and volume of post-vaccination blood draws are provided in section 3.5.
- The site should schedule the next study activity (safety phone call) with the subject.
- The subject will receive a written reminder of the next planned study activity. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

5.3.2 Safety Follow-up Calls

Safety follow-up calls will be performed on Day 22 (Visit 5), Day 209 (Visit 10) and Day 271 (Visit 11) and include the following procedures:

- Safety follow-up calls are calls made to the subject by a healthcare professional designated on the site log. These calls will follow a script which will facilitate the collection of relevant safety information. The subject will be interviewed according to the script, and information relating to solicited local and systemic AEs persisting beyond Day 14 and unsolicited adverse events including SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal, and/or NOCD and concomitant medications or vaccinations associated with those events. All safety information described by the subject must be written down in a designated location within the source document and not written on the script used for the telephone call.
- The site should schedule the next study activity (clinic visit or study termination visit) with the subject.
- The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

5.4 Unscheduled Visits

An unscheduled visit describes a non-routine study visit triggered by a specific event. These could include anticipated or unanticipated adverse events or interventions.

The following procedures should be carried out for all unscheduled visits:

1. Evaluate the subject's vital signs body temperature, heart rate, and blood pressure and perform a symptom-directed physical examination.
2. Record any observed AEs in the source documents.
3. Record any concomitant medications or vaccinations associated with AEs in the source documents.

5.5 Study Termination Visit

The study termination visit is scheduled on Day 366 (Visit 12). The termination visit is a clinic visit. For visit procedures to be performed for a subject whose planned study participation ends prematurely, please see section 5.5.1.

At the Study Termination clinic visit the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit.
- The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present.
- Medically attended AEs, SAEs, NOCDs, or AESIs will be recorded on source documents.
- All medications taken or vaccines received will also be recorded on the source documents.
- The site will review with the subject the plan of when information relating to the subject's participation in the study may be available (e.g., study results, treatment assignments). It will also be discussed how information relating to the subject's participation in the study will be shared with the subject's healthcare provider, if the subject chooses to share this information.
- The site will complete the termination CRF page and this will mark the completion of the subject's participation in the study.

5.5.1 Early Termination Visit

The date of termination is the date of the last contact in which the subject's health status was assessed or, in cases where the subject does not agree to any further safety follow-up, it is the date consent is withdrawn. This date should be recorded on the appropriate CRF page.

When a subject is withdrawn from treatment or withdraws from the study, the investigator will notify the Sponsor and, when possible, will perform the procedures listed below.

The reason(s) for the early termination must be included in the subject's source documentation. If the Early Termination Visit is a telephone call, collect as much information as possible. Early Termination Visits include subjects who were randomized but not treated.

At the clinic visit or during the telephone call, the following procedures should be performed, when possible:

- Collection and review of Subject Diary (if not already collected).
- Interview of subject to collect unsolicited adverse events, medically attended AEs, AEs leading to withdrawal, SAEs, AESIs, and NOCD.
- Interview of subject to collect concomitant medications and/or vaccinations.
- Symptom-directed physical assessment, at least including measurement of vital signs (body temperature, respiratory rate, blood pressure, heart rate) and a check of general appearance (in case of clinic early termination visit).
- Draw a blood sample (approximately 10 ml) and a urine sample for Safety Laboratory assessment (in case of clinic early termination visit).
- The site will review with the subject the plan of when information relating to the subject's participation in the study may be available (e.g., study results, treatment assignments). It will also be discussed how information relating to the subject's participation in the study will be shared with the subject's healthcare provider, if the subject chooses to share this information.
- The site will complete the appropriate CRF page and this will mark the completion of the subject's participation in the study.

6.0 TREATMENT OF SUBJECTS

All vaccines associated with this study are to be stored separately from other vaccines and medications in a secure location under appropriate storage conditions with temperature monitoring. **All vaccines associated with this study must be checked for expiration date prior to use. Expired vaccines must not be administered to subjects.**

6.1 Study Vaccine(s)

The term 'study vaccine' refers to those vaccines provided by the Sponsor, which will be evaluated as part of the study objectives. The study vaccines specific to this study are described in Table 6.1-1.

Table 6.1-1: Study Vaccine Composition

Group A (Control) Meningococcal C-CRM$_{197}$ Conjugate Vaccine	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM$_{197}$ protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
Sodium Chloride	3.5 mg
Sterile water for injection, up to	0.5 ml

Group B (12.5µg LHD153R) - MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	

Meningococcal C oligosaccharide conjugated to	10 µg
CRM_{197} protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide/LHD153R Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
LHD153R	12.5 µg
Sodium Chloride	3.4 mg
Histidine	0.1 mg
Tris	30 µg
Sterile water for injection, up to	0.5 ml
Group C (25 µg LHD153R) - MenC-CRM_{197}/Aluminium Hydroxide/LHD153R	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM_{197} protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide/LHD153R Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
LHD153R	25 µg
Sodium Chloride	3.4 mg
Histidine	0.2 mg
Tris	61 µg
Sterile water for injection, up to	0.5 ml

Group D (50µg LHD153R) - MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM$_{197}$ protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide/LHD153R Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
LHD153R	50 µg
Sodium Chloride	3.2 mg
Histidine	0.4 mg
Tris	121 µg
Sterile water for injection, up to	0.5 ml
Group E (100µg LHD153R) - MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM$_{197}$ protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg

Aluminum Hydroxide/LHD153R Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
LHD153R	100 µg
Sodium Chloride	2.9 mg
Histidine	0.8 mg
Tris	243 µg
Sterile water for injection, up to	0.5 ml

6.2 Non-Study Vaccines

The term 'non-study vaccine' refers to those vaccines which will be intentionally given to study subjects but not formally included in the analysis of study objectives.

No non-study vaccines are planned for this study. Any non-study vaccines administered during the study conduct will be captured in the CRF as concomitant medications and/or vaccinations.

6.3 Vaccine Preparation and Administration

The investigator or designee will be responsible for oversight of the administration of vaccine to subjects enrolled in the study according to the procedures stipulated in this study protocol. All vaccines will be administered only by unblinded personnel who are qualified to perform that function under applicable local laws and regulations for the specific study site.

The vaccine components will be provided in 5 separate kits (i.e. one for the control and one for each of the 4 dosage groups). The vaccine components must be mixed prior to vaccination taking into account the appropriate aseptic procedures. Detailed vaccine preparation and administration instructions, including the maximal administration period, will be provided to investigators prior to study start and must be filed in the Investigator Site File.

PRECAUTIONS TO BE OBSERVED IN ADMINISTERING STUDY VACCINE:

- Prior to vaccination, subjects must be determined to be eligible for study vaccination and it must be clinically appropriate in the judgment of the investigator to vaccinate. Eligibility for vaccination prior to first study vaccine administration is determined by evaluating the entry criteria outlined in protocol sections 4.0.

- Study vaccines must not be administered to individuals with known hypersensitivity to any component of the vaccines.

- Standard immunization practices are to be observed and care should be taken to administer the injection intramuscularly. Before administering vaccine, the vaccination site is to be disinfected with a skin disinfectant (e.g., 70% alcohol). Allow the skin to dry. **DO NOT inject intravascularly**.

- As with all injectable vaccines, trained medical personnel and appropriate medical treatment must be readily available in case of anaphylactic reactions following vaccine administration. For example, epinephrine 1:1000, diphenhydramine, and/or other medications for treating anaphylaxis should be available.

6.4 Vaccine Administration Error or Overdose of Vaccine

Vaccine administration error is defined as receiving a dose of study vaccine that was not reconstituted as instructed or administered by a different route from the intended route of administration. An overdose of study vaccine (whether accidental or intentional) is defined when a dosage higher than the recommended dosage is administered in one dose of study vaccine.

Any vaccine administration error or overdose of study vaccine detailed in this protocol must be reported as an adverse event, and if the vaccine administration error or overdose is associated with a serious adverse event, it must be reported as such within 24 hours to the Sponsor.

6.5 Prior and Concomitant Medications and Vaccines

All medications, vaccines and blood products taken or received by the subject within 180 days prior to the start of the study are to be recorded in the appropriate CRF.

Medications taken for prophylaxis are those intended to prevent the onset of symptoms. Medications taken for treatment are intended to reduce or eliminate the presence of symptoms that are present.

NOTE: Use of antipyretics/analgesics within 24 hours prior to vaccine administration is a reason to delay study vaccination (see section 4.3).

Concomitant medications include all medications (including vaccines) taken by/administered to the subject at and after enrolment and must be documented in the appropriate CRF.

When recording concomitant medications/vaccines, they should be checked against the study entry criteria in section 4.0, to ensure that the subject should be enrolled in the study.

6.6 Vaccine Supply, Labeling, Storage and Tracking

The Sponsor will ensure the following:

- Supply the study vaccines.
- Appropriate labeling of all study vaccines provided that complies with the legal requirements of each country where the study is to be performed.

The investigator must ensure the following:

- Acknowledge receipt of the study vaccines by a designated staff member at the site, including:
  - Confirmation that the vaccines were received in good condition
  - Confirmation to the Sponsor of the temperature range during shipment from the Sponsor to the investigator's designated storage location
  - Confirmation by the Sponsor that the vaccines are authorized for use.
- Proper storage of the study vaccines, including:
  - Storage in a secure, locked, temperature-controlled location.
  - Proper storage according to the instructions specified on the labels.
  - Appropriate record keeping and inventory of the study vaccines, including regular documentation of adequate storage temperature.
- Appropriate use of the study vaccines, including:
  - No use of vaccines prior to receipt of authorization for use from the Sponsor.
  - Use only in accordance with the approved protocol.
  - Proper handling, including confirmation that the vaccine has not expired prior to administration.
  - Appropriate documentation of administration of vaccines to study subjects including:
    - Date, dosage, batch/lot numbers, expiration dates, unique identifying numbers assigned to subjects and study vaccines, and time of vaccine

administration. This information will be maintained in an accountability log that will be reviewed by the site monitor.

- Reconciliation of all vaccines received from the Sponsor. Reconciliation is defined as maintaining records of which and how many vaccines were received, which vaccines were administered to subjects, which vaccines were destroyed at the site, and which vaccines were returned to the Sponsor, as applicable.

- Proper adherence to the local institutional policy with respect to destruction of study vaccines.
- Complete record keeping of vaccine use, wastage, return or destruction, including documentation of:
  - Copy of the site's procedure for destruction of hazardous material.
  - Number of doses destroyed, date of destruction, destruction code (if available), method of destruction, and name of individual performing destruction.

Vaccines that have been stored differently from the manufacturer's indications **must not** be used unless the Sponsor provides written authorization for use. In the event that the use cannot be authorized, the Sponsor will make every effort to replace the vaccine supply. All vaccines used in conjunction with this protocol must be stored separately from normal hospital/practice stocks to prevent unintentional use of study vaccines outside of the clinical study setting.

Monitoring of vaccine accountability will be performed by the study monitor during site visits and at the completion of the study.

At the conclusion of the study, and as appropriate during the course of the study, the investigator must ensure that all unused study vaccines, packaging and supplementary labels are destroyed locally (upon approval from Sponsor) or returned to the Sponsor.

7.0 ASSESSMENTS

7.1 Safety Assessment

The measures of safety used in this study are based on previous study data and based on comparable routine clinical/laboratory procedures. They include a close vigilance for, and stringent reporting of selected local and systemic adverse events routinely monitored in vaccine studies as indicators of reactogenicity.

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

The period of observation for AEs extends from the time the subject signs informed consent until he or she completes the specified safety follow-up period (Day 366) or terminates the study early (whichever comes first). AEs occurring after the informed consent form is signed but prior to receiving study vaccine/product will be documented as an adverse event and recorded within the source documents. However, any AEs occurring prior to receipt of any study vaccine will be analyzed separately from “treatment emergent” AEs (AEs occurring after administration of the first study vaccine).

Adverse events are collected as either solicited or unsolicited adverse events. Solicited events are derived from organized data collection systems, such as Subject Diaries or interview.

7.1.1 Solicited Adverse Events

The term “reactogenicity” refers to solicited signs and symptoms (“solicited adverse events”) occurring in the hours and days following a vaccination, to be collected by the subject after the first 24 hours inpatient observation period at Day 1until Day 14, using a pre-defined Subject Diary.

The following solicited adverse events are included in the Subject Diary. Each adverse event is to be assessed using the scoring system shown in Appendix A (Solicited Local AEs) and Appendix B (Solicited Systemic AE):

Solicited Local Adverse Events

Solicited local AEs include:

- injection site erythema
- injection site induration
- injection site pain
- injection site swelling **Solicited Systemic Adverse Events**

Solicited systemic AEs include:

- body temperature ≥38.0°C (as measured orally)
- loss of appetite
- nausea
- fatigue
- generalized myalgia
- generalized arthralgia
- headache
- chills
- vomiting
- diarrhea
- generalized rash
- urticaria

Other Solicited Data

Other solicited data collected per Subject Diary include:

- Use of analgesics/antipyretics recorded as “absent” or “present” and summarized by “for treatment” or “for prophylaxis”
- Body temperature as recorded daily, ideally at same time, by the oral route

The study staff must review the data entered into the Subject Diary as described in sections 3.4.2 and 5.3.1.

NOTE: Any solicited adverse event that meets any of the following criteria must be entered into the subjects' source documents (see section 9.1) and also as an adverse event in the appropriate CRF:

- Solicited local or systemic adverse event that continues beyond Day 14 after vaccination.
- Solicited local or systemic adverse event that leads to a visit to a healthcare provider (medically attended adverse event, see section 7.1.3).
- Solicited local or systemic adverse event leading to the subject withdrawing from the study or the subject being withdrawn from the study by the investigator (adverse event leading to withdrawal, see section 7.1.3).
- Solicited local or systemic adverse event that otherwise meets the definition of a serious adverse event (see section 7.1.4).

7.1.2 Unsolicited Adverse Events

An unsolicited adverse event is an adverse event that was not solicited using a Subject Diary and that was spontaneously communicated by a subject who has signed the informed consent.

7.1.3 Evaluation of Adverse Events

Every effort should be made by the investigator to evaluate safety information reported by a subject for an underlying diagnosis and to capture this diagnosis as the event in the AE page. In other words, the practice of reporting only symptoms (e.g., "cough" or "ear pain") are better reported according to the underlying cause (e.g., "asthma exacerbation" or "otitis media").

The severity of events reported on the appropriate CRF page will be determined by the investigator as:

Mild: transient with no limitation in normal daily activity.
Moderate: some limitation in normal daily activity.
Severe: unable to perform normal daily activity.

The relationship of the study treatment to an AE will be determined by the investigator based on the following definitions:

1. Not Related

The AE is not related to an investigational vaccine if there is evidence that clearly indicates an alternative explanation. If the subject has not received the vaccine, the timing of the exposure to the vaccine and the onset of the AE are not reasonably related in time, or other facts, evidence or arguments exist that reasonably suggest an alternative explanation, then the AE is not related.

2. Possibly Related

The administration of the investigational vaccine and AE are considered reasonably related in time and the AE could be explained by exposure to the investigational vaccine or by other causes.

3. Probably Related

Exposure to the investigational vaccine and AE are reasonably related in time and no alternative explanation has been identified.

The relationship of the study treatment to an unsolicited AE will be determined by the investigator.

Note: solicited AEs will not be evaluated for relationship to study treatment. Grading for severity of solicited local and systemic AEs is described in Appendix A and Appendix B.

Adverse events will also be evaluated by the investigator for the co-existence of any of the other following conditions:

- "Medically attended adverse event": an adverse event that leads to a visit to a healthcare provider.
- "New onset of chronic disease" (NOCD): an adverse event that represents a new diagnosis of a chronic medical condition that was not present or suspected in a subject prior to study enrolment.
- AEs leading to withdrawal: adverse events leading to study or vaccine withdrawal.

All AEs, regardless of severity, will be monitored until resolution or until the investigator assesses them as chronic or stable. All subjects experiencing AEs - whether considered associated with the use of the study vaccine or not - must be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible.

7.1.4 Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose results in one or more of the following:

- Death.
- Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe.
- Required or prolonged hospitalization.
- Persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions).
- Congenital anomaly/or birth defect.
- An important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

Adverse events which do not fall into these categories are defined as non-serious.

It should be noted that a severe adverse event need not be serious in nature and that a serious adverse event need not, by definition, be severe.

Serious adverse events will be captured both on the Vaccines Serious Adverse Event (VSAE) form as well as on the appropriate CRF page. All SAEs will be evaluated by the investigator for relationship of the event to study vaccine. SAEs that are judged to be possibly or probably related to the study vaccine should be reported to the Sponsor as related/suspected events.

The relationship of the study treatment to an SAE will be determined by the investigator based on the following definitions:

1. Related/suspected

The SAE is judged by the investigator to be possibly or probably related to the study vaccine on the appropriate CRF page (see section 7.1.3).

2. Not Related

The SAE is not related if exposure to the study vaccine has not occurred, **or** the occurrence of the SAE is not reasonably related in time, **or** the SAE is considered unlikely to be related to use of the study vaccine, i.e., there are no facts (evidence) or arguments to suggest a causal relationship.

The relationship of the study vaccine to an SAE will be determined by the investigator.

In addition, SAEs will be evaluated by the Sponsor or designee for "expectedness." An unexpected AE is one that is not listed in the current Summary of Product Characteristics or the Investigator's Brochure or an event that is by nature more specific or more severe than a listed event.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the appropriate CRF. If the onset of an event occurred before the subject entered the study (e.g., any pre-planned hospitalization for conditions like cosmetic treatments or for non-emergency routine visits for a pre-existing condition), the hospitalization would not lead to an AE being classified as serious unless, in the view of the investigator, hospitalization was prolonged as a result of participation in the clinical study or was necessary due to a worsening of the pre-existing condition.

7.1.4.1 Adverse Events of Special Interest

Certain adverse events of special interest (AESIs) are monitored after the administration of immunostimulatory agents. All subjects enrolled in this study will be monitored for AESIs for the entire follow-up period. The AESIs will be defined according to MedDRA preferred terms. The investigator will be provided with a list of AESIs prior to study start. Receipt of this list will be notified and stored, along with the list of AESIs, in the Investigator Site File. During the course of the trial the list of AESIs may change. If this occurs, the investigators will be advised of the change and confirmation of receipt will be documented. The updated list of AESIs and documentation of receipt are also stored in the Investigator Site File. The occurrence of any of these adverse events will be treated as a serious adverse event (SAE), meeting the criterion of a "medically important event."

Subjects will be assessed for diagnosis of an AESI at the following visits:

- Pre-vaccination clinic visit (Day -28 to Day -3)
- Visit 1 (Day 1, pre-vaccination)
- Visit 2 (Day 4)

- Visit 3 (Day 8)
- Visit 4 (Day 15)
- Visit 5 (Day 22; Safety Follow-Up Call)
- Visit 6 (Day 29)
- Visit 7 (Day 85)
- Visit 8 (Day 113)
- Visit 9 (Day 181)
- Visit 10 (Day 209; Safety Follow-Up Call)
- Visit 11 (Day 271; Safety Follow-Up Call)
- Visit 12 (Day 366; Study Termination Visit)

At these visits a qualified health care practitioner listed on the site's responsibilities and delegation logs will conduct a review of organ systems and a targeted physical exam and will evaluate subjects for any new signs or symptoms that could indicate one of the AESIs as specified in the list of AESIs stored in the Investigator Site File. They will also interview the subject about recent medical history and any new diagnosis that could indicate an AESI. Medical records related to any new medical event or diagnosis will be requested, reviewed by the site staff, and recorded in the subject's source documents.

A diagnosis of an AESI will be reported in the same manner and time frame as an SAE using the VSAE form. The investigator must notify Novartis within 24 hours. The AESI diagnosis, as well as any medications taken to treat the condition, will be recorded in the subject's source documents and on the appropriate CRF.

7.1.5 Methods for Recording Adverse Events and Serious Adverse Events

All findings regarding Adverse Events must be reported on the appropriate CRF page and on the VSAE form, if applicable, which is part of the Investigator Site File. All findings in subjects experiencing AEs must be reported also in the subject's source document.

All SAEs which occur during the course of the study, whether considered to be associated with the study vaccination or not, must be reported **within 24 hours of the site becoming aware of the event** to Novartis or its designee. Specific instructions and contact details for collecting and reporting SAEs to Novartis will be provided to the investigator.

All SAEs are also to be documented on the appropriate CRF page. Any medication or other therapeutic measures used to treat the AE will be recorded on the appropriate CRF(s) in addition to the outcome of the AE.

After receipt of the initial report, representatives of Novartis or its designee will contact the investigator if it is necessary to obtain further information for assessment of the event.

All SAEs must be reported by the investigator to his/her corresponding EC and applicable regulatory authorities in accordance with institutional policy/regulatory requirements and adequate documentation of this notification must be provided to the Sponsor.

Novartis or its designee must also comply with the applicable regulatory requirement(s) related to the reporting of suspected unexpected serious adverse vaccine reactions (also known as SUSARs) to the regulatory authority(ies) and the IRB/EC. If a SUSAR or other safety signal relating to use of one of the study vaccines is reported to Novartis or its designee, the Sponsor will communicate the information to the investigator and the investigator will be responsible for submitting this information to the EC and other relevant authorities.

7.1.5.1 Post-Study Events

Any suspected SAE that occurs outside of the protocol-specified follow-up period or after the end of the study but considered to be caused by the study vaccine must be reported to Novartis or its designee. These SAEs will be processed by Novartis or its designee as during the course of the study, until 3 months after the last scheduled study visit. Instructions and contact details for collecting and reporting these suspected SAEs will be provided to the investigator.

7.1.6 Pregnancies

To ensure subjects' safety, each pregnancy in a subject after study vaccination must be reported to Novartis within 72 hours of the site learning of its occurrence. If the subject agrees to submit this information, the pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if intended duration of safety follow-up for the study has ended.

Pregnancy data must be recorded on a Pregnancy Report CRF (initial report) and Pregnancy Follow-Up CRF (outcome report).

Any pregnancy outcome meeting the definition of a SAE (see section 7.1.4) must also be reported on the VSAE Report Form.

7.1.7 Safety Laboratory Measurements

Blood and urine samples will be collected from all subjects at the Pre-vaccination Screening, at Visit 1, at Visit 3 and at Visit 6 as outlined in Time and Events Table 3. The blood safety laboratory assessments will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, liver function tests (ALT, AST), a complete blood count and C-reactive protein. The urine safety laboratory assessments will include protein, glucose and red blood cells. An additional blood and urine sample will be collected in case of a clinic Early Termination Visit as outlined in section 5.5.1.

All testing will be conducted by qualified and certified laboratories. Abnormal laboratory values will be defined following the FDA CBER Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" dated September 2007, or the institution's normal ranges if they differ from CBER guidance. Please see Appendix C, D and E for further details on the Toxicity Grading Scales according to CBER.

Retesting may be performed in case of abnormal values per guidance of the investigator. Retest results will not be captured in the CRF.

7.2 Efficacy Assessment

Efficacy measurement will not be performed as part of this study.

7.3 Immunogenicity Assessment

The measures to assess the primary and secondary immunogenicity endpoints for this study are standard, i.e., widely used and generally recognized as reliable, accurate, and relevant (able to describe the quality and extent of the immune response).

The assay's used in this study to assess the primary and immunogenicity endpoints are human serum bactericidal assay (hSBA) and ELISA specific for MenC

The hSBA is a functional measure of the ability of specific antibodies, in conjunction with human complement, to kill MenC indicator strains, and is widely used and generally recognized as the serological correlate of protection. The specific ELISA will be used to measure the induction of antibodies directed against MenC following vaccination with the study vaccines.

Blood samples (approximately 10 ml) to obtain serum for hSBA and ELISA assays will be collected at Day 1, Day 8, Day 29 and Day 181 (refer to section 3.5 for detailed specimen collection procedures).

Testing will be conducted by a Novartis or designated laboratory in a blinded manner towards the treatment group. Laboratory contact details are listed in the Protocol Ancillary Document.

All data will be captured at the laboratory and transferred via Electronic Data Transfer (EDT)

Details on all blood sample handling steps are described in the Clinical Specimen Lab Manual provided to the study site.

7.4 Exploratory Measurements

In those subjects who agree to a separate Informed Consent, additional blood samples will be collected at Day 1, Day 4, Day 8, Day 29 and Day 181 for exploratory measurements. The purpose of these exploratory measurements is to assess the systemic exposure of LHD153, to further delineate vaccine induced antigen specific immune responses and to evaluate biomarkers that may be predictive for safety and/or innate immune activation.

All exploratory measurements will be conducted by a Novartis or a designated laboratory. Laboratory contact details are listed in the Protocol Ancillary Document.

Exploratory measurements may be performed after the Clinical Study Report (CSR) has been completed, in which case these data will be submitted as an addendum to the CSR.

Systemic exposure of LHD153

Systemic exposure of LHD153 will be assessed by analyzing LHD153 blood plasma levels at Day 1 (baseline, 1, 2, 4, 8 and 24h after vaccination) and Day 4 using LC/MS/MS. Time-points for assessment of clinical exposure of LHD153 have been selected based on non-clinical data in dogs and rats.

Vaccine-induced antigen-specific immune responses

The frequency of B cells specific for MenC polysaccharide and CRM_{197} will be determined by enzyme-linked immunosorbent spot (ELISPOT) at Day 1, Day 8, Day 29 and Day 181 in order to evaluate the baseline specific B-cell frequency (Day 1), the peak of plasmablast responses (Day 8), the peak of B cell memory responses (Day 29), and the persistence of memory B cell responses (Day 181).

Subsequently, the diversity of the antigen specific B-cell repertoire as well as the specific antibody functionality will be analyzed in a selected subset of subjects. The selection of the subset will be based on the most pronounced response to the study vaccines when compared to baseline as determined by the primary and secondary immunogenicity assessment.

The diversity of the elicited B-cell receptors will be assessed through sequence analysis of complementary DNA (cDNA) generated from immunoglobulin (Ig) messenger RNA (mRNA). The Ig cDNAs will be analyzed from antigen-specific B cells obtained at Day 1, Day 29 and/or Day 181 and plasmablasts isolated at Day 8. The analysis of the B-cell receptor diversity does not have the intent nor the capability to identify or rule out any genetic modifications in the RNA or DNA that are presumably linked to disease or predisposition to disease.

To evaluate the functionality specific antibodies induced by the study vaccines, biochemical and cell-based assays will be performed on a selected subset of serology samples collected for the assessment of the primary and secondary immunogenicity endpoints at Day 1, Day 8, Day 29 and Day 181. The evaluation of antigen specific antibody functionality includes determination of the antibody isotype and the antibody glycosylation state. Furthermore, the ability of the MenC-specific antibodies to fix complement, to promote antibody-dependent cell mediated cytoxicity (ADCC), to induce phagocytosis and to activate FcR+ cells in vitro will be assessed. If the quantity of serum available for this specific exploratory objective is limited, assessments of isotype, glycosylation state and complement fixing capacity will be prioritized over the other assessments.

The frequency of T cells specific for the CRM_{197} protein at baseline (Day 1), at Day 8 and at Day 29 after vaccination with the study vaccines will be determined by FACS analysis using intracellular staining with a panel of cytokines and surface markers to identify cell populations.

Early Markers for Safety and Innate immune activation

The evaluation of potential biomarkers of safety and innate immune activation will be performed on blood specimens collected at Day 1 (baseline, 6h and 24h after vaccination) and Day 4.

The vaccine-induced production of inflammatory cytokines and chemokines will be monitored on serum samples using a commercially available electrochemoluminescence assay for a panel of pro-inflammatory cytokines and chemokines, including Eotaxin, Eotaxin-3, GM-CSF, IFN-g, IL-1a, IL-1b, IL-10, IL-12 p70, IL-12/IL-23p40, IL-13,

IL15, IL-16, IL-17A, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-8 (HA), IP-10, MCP-1, MCP-4, MDC, MIP-1a, MIP-1b, TARC, TNF-a, TNF-b, VEGF.

The vaccine-induced expression of genes and gene families will be monitored on whole blood samples using of RNA microarrays by existing technologies. The RNA micro array analysis does not have the intent nor the capability to identify or rule out any genetic modifications in the RNA or DNA that are presumably linked to disease or predisposition to disease.

8.0 STATISTICAL CONSIDERATIONS

8.1 Endpoints

8.1.1 Primary Endpoint(s)

8.1.1.1 Primary Safety Endpoint(s)

The measures for assessing safety and tolerability (by vaccine group within each cohort and by LHD153R adjuvant dosage group overall) are as follows:

- The frequency and percentage of subjects with solicited local and systemic AEs through Day 14. Time intervals after vaccination that will be summarized are:30 minutes post-vaccination, Days 1-4 (without 30 minutes), Days 5-8, Days 8-14, Days 1-8 (without 30 minutes) and Days 1-14 (without 30 minutes).
- The frequency and percentage of subjects with any unsolicited AEs from the day of vaccination (Day 1) to Day 14.
- The frequency and percentage of subjects with SAEs, medically attended AEs, AEs leading to study withdrawal, NOCDs, AESIs for the following time periods: day of signed informed consent until study completion (Day 366), day of vaccination (Day 1) to Day 29, and Day 29 to study completion (Day 366).
- The absolute values and changes in hematology, chemistry, and urinalysis parameters (see section 7.1.7).
- The frequency and percentage of subjects with abnormal laboratory parameter values

as classified by investigator normal ranges (low, normal, high) and as classified by CBER toxicity grading scales, when available.

8.1.1.2 Primary Efficacy Endpoint(s)

Not applicable.

8.1.1.3 Primary Immunogenicity Endpoint(s)

The primary immunogenicity endpoints are the GMTs measured by hSBA directed against MenC from samples collected on Day 1 (baseline, before vaccination) and Day 29 as well as the GMR of the titers (Day 29 / Day 1).

8.1.2 Secondary Endpoint(s)

8.1.2.1 Secondary Safety Endpoint(s)

Not applicable.

8.1.2.2 Secondary Efficacy Endpoint(s)

Not applicable.

8.1.2.3 Secondary Immunogenicity Endpoint(s)

The secondary immunogenicity endpoints are:

- GMTs and corresponding GMRs measured by hSBA directed against MenC for samples collected at Day 8 and Day181.
- Percentage of subjects with hSBA seroresponse at Days 8, 29, and 181. Seroresponse is defined as a post vaccination hSBA ≥8 for subjects with a baseline hSBA <4 or have an increase of at least 4 times the baseline hSBA level for subjects with prevaccination hSBA ≥4.
- Antibody geometric mean concentrations (GMCs) against MenC measured by ELISA for samples collected on Days 1 (baseline, prior to vaccination), 8, 29, and 181.
- The percentage of subjects with at least a 4-fold increase in antibody concentrations to MenC as measured by ELISA on Day 8, 29, and 181 relative to baseline (Day 1).

8.1.3 Exploratory Endpoint(s)

The exploratory endpoints are based on results of testing which may not be performed until after the study report has been finalized and will be further refined prior to testing. They include the following:

- Serum concentration of LHD153 at Day 1 baseline (prior to vaccination), Day 1 (1h , 2h, 4h, 8h, and 24h after vaccination), Day 4 by LC-MS/MS.
- Frequency of MenC polysaccharide-specific and CRM_{197}-specific B cells at Day 1 (baseline), Day 8, Day 29, and Day 181 by ELISPOT.
- Diversity of MenC polysaccharide-specific B-cell repertoire at Day 1 (baseline), Day 8, Day 29, and Day 181 by immunoglobulin cDNA sequencing.
- Functionality of antigen specific antibodies will be assessed at Day 1 (baseline), Day 8, Day 29, and Day 181 by analysis of immunoglobulin isotype, glycosylation state and their ability to fix complement, to promote antibody-dependent cell mediated cytoxicity, to induce phagocytosis and to activate FcR+ cells. If the quantity of serum available for this specific exploratory objective is limited, assessments of immunoglobulin isotype, glycosylation state and complement fixing capacity will be prioritized over the other assessments.
- Frequency and quality of T cells specific for CRM_{197} at Day 1 (baseline), Day 8, and Day 29 by fluorescence activated cell sorting (FACS) analysis using intracellular staining with a wide panel of cytokines and surface markers to identify cell populations.
- Serum concentrations of a panel of 30 chemokines and cytokines at Day 1 baseline (prior to vaccination), Day 1 (6h and 24h after vaccination), Day 4, and Day 8 by multiplex Electro-chemo-luminescence based assay.
- Gene expression profile in whole blood at Day 1 baseline (prior to vaccination), Day 1 (6h and 24h after vaccination), Day 4, and Day 8 by RNA micro array analysis.

8.2 Success Criteria

The study has no formal statistical hypotheses and will not be declared positive or negative according to given rules. The selection of an appropriate LHD153R adjuvant dosage for future studies will be determined by the joint evaluation of the immunogenicity and safety profiles of each dosage group. **8.2.1 Success Criteria for Primary Objective(s)** Not applicable.

8.2.2 Success Criteria for Secondary Objective(s)

Not applicable.

8.3 Analysis Sets

8.3.1 All Enrolled Set

All screened subjects who provide informed consent and provide demographic and/or baseline screening assessments, regardless of the subject's randomization and treatment status in the study and received a Subject ID.

8.3.2 All Exposed Set

All subjects in the enrolled set who receive a study vaccination.

8.3.3 Safety Set

Safety Set (solicited adverse events and other solicited reactions)

All subjects in the Exposed Set who:

- Provide post vaccination reactogenicity data.

Safety Set (unsolicited adverse events)

All subjects in the Exposed Set who:

- Have post-vaccination unsolicited adverse event records.

Safety Set (overall)

All subjects in the Exposed Set who:

- Have either post-vaccination adverse event or reactogenicity records.

Subjects will be analyzed as "treated" (i.e., according to the vaccine a subject received, rather than the vaccine to which the subject may have been randomized).

8.3.4 Full Analysis Set (FAS) Efficacy/Immunogenicity Set

All subjects in the Enrolled Set who:

- Receive a study vaccination AND provide efficacy/immunogenicity data at relevant time points.

FAS sets will be analyzed “as randomized” (i.e., according to the vaccine a subject was designated to receive, which may be different from the vaccine the subject actually received).

8.3.5 Per Protocol (PP) Set Efficacy/Immunogenicity Set

All subjects in the FAS efficacy/immunogenicity set who:

- Are not excluded due to reasons (see section 8.3.8) defined prior to unblinding or analysis.

PPS are subsets of FAS and should always be defined even if the objectives do not require it.

Examples for subjects excluded due to other reasons than protocol deviations are:

- Subjects who withdrew informed consent.
- Premature withdrawal due to an adverse event.

Exclusions need to be considered by objective/time point, i.e., sometimes not all data of a subject but only part of the subject's data will be removed from the PPS analysis.

8.3.6 Other Analysis Sets

All subjects in the Enrolled Set who consent to additional blood draws, receive a study vaccination AND provide exploratory assay data at relevant time points will be included in an exploratory assay subset.

8.3.7 Subgroups

Selected immunogenicity analyses may be provided based on seropositivity status at baseline.

8.3.8 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. A protocol deviation may be a reason to remove data from an analysis set at the time of analysis. Reportable protocol deviations will be defined as exclusionary from the analysis according to protocol objectives and endpoints, which will be specified in the Statistical Analysis Plan. In some cases exclusion of data may be due to a reason other than a protocol deviation, e.g. early termination.

8.4 Statistical Analysis Plan

This section provides a summary of the statistical methodology to be used. A more detailed description of analysis methods will be provided in a separate Statistical Analysis Plan which may also include additional exploratory analyses not explicitly mentioned in the following sections.

8.4.1 Analysis of Demographic and Baseline Characteristics

Descriptive statistics (number of non-missing observations, mean, standard deviation, median, minimum and maximum) for age, height and weight at enrolment will be calculated overall and by vaccine group and LHD153R adjuvant dosage.

Distributions of subjects by sex and ethnic origin will be summarized overall and by vaccine group and LHD153R adjuvant dosage.

8.4.2 Analysis of Primary Objective(s)

8.4.2.1 Analysis of Primary Safety Objective(s)

Safety of the study vaccines will be assessed in all subjects in terms of the frequency and percentage of reported AEs as well as by changes in clinical laboratory values.

8.4.2.1.1 Analysis of Extent of Exposure

The frequency and percentage of subjects with vaccinations will be summarized by vaccine group and LHD153R adjuvant dosage, by cohort and overall, for the Enrolled Set.

8.4.2.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events

All solicited adverse events will be summarized according to defined severity grading scales. Use of medication to prevent/treat fever will be summarized according to frequencies and percentages reporting “Yes” and “No”.

Frequencies and percentages of subjects experiencing each adverse event will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic adverse event overall and at each time point will also be presented.

Post-vaccination solicited adverse events reported from Day 1 to Day 14 will be summarized for the intervals Day 1-4 (without 30 minutes), Day 5-8, Day 1-8 (without 30 minutes), Day 8-14 and Day 1-14 (without 30 minutes) by maximal severity and by

vaccine group and LHD153R adjuvant. The severity of solicited local adverse events, including injection-site erythema, swelling and induration will be summarized according to categories based on linear measurement: 25-50 mm, 51-100 mm, > 100 mm.

Injection site pain and systemic reactions (except fever) occurring up to Day 14 will be summarized according to “mild”, “moderate” or “severe”.

Each solicited local and systemic adverse event will also be further summarized as “none” versus “any”.

Implausible measurements (for further definition see Statistical Analysis Plan) will be left out of the analysis.

Use of antipyretics and analgesics will be summarized by frequency by type of use (prophylactic versus treatment) and percentage of subjects reporting use. The influence of antipyretics and analgesics use on the occurrence of specific adverse events (e.g., fever, pain) will be assessed.

Body temperature will be summarized by 0.5 °C and 1.0 °C increments from 36.0 °C up to ≥40 °C.

8.4.2.1.3 Analysis of Unsolicited Adverse Events

This analysis applies to all adverse events occurring during the study, judged either as probably related, possibly related, or not related to vaccination by the investigator, recorded in the CRF, with a start date on or after the date of first vaccination. AE starting prior to the first vaccination will only be listed. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class.

All reported adverse events, as well as adverse events judged by the investigator as at least possibly related to study vaccine, will be summarized according to system organ class and preferred term within system organ class. These summaries will be presented by vaccination group and LHD153R adjuvant dosage for each cohort and by interval of study observation. When an adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted.

Separate summaries will be produced for the following categories:

- Serious adverse events.

- Adverse events that are possibly or probably related to vaccine.
- Adverse events of special interest.
- New onset of chronic disease.
- Adverse event leading to withdrawal.
- Adverse events leading to a medically attended visit.
- Adverse event by data source.

Data listings of all adverse events will be provided by subject. In addition, adverse events in the categories above will be provided as listed data.

8.4.2.1.4 Analysis of Safety Laboratory Values

The investigator must review all safety laboratory results (see Section 7.1.7). Abnormal laboratory values and clinically significant changes in values from pre-vaccination (Screening Visit) will be assessed, using medical judgment, based on the FDA CBER Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" dated September 2007, or the institution's normal ranges if they differ from CBER guidance. Please see Appendix C, D and E for further details.

The following information will be provided:

- Change in absolute laboratory value from pre-vaccination (Screening Visit) and Day 1 (Visit 1) baseline to Day 8 (Visit 3) and Day 29 (Visit 6) after vaccination.
- The classification of laboratory values and/or their changes from pre-vaccination according to the CBER toxicity grading scale.
- 3 x 3 shift tables by visit using the categorization of laboratory values according to institutional normal reference ranges (below, within, above).

8.4.2.2 Analysis of Primary Efficacy Objective(s)

Not applicable.

8.4.2.3 Analysis of Primary Immunogenicity Objective(s)

8.4.2.3.1 Statistical Hypotheses

There are no statistical hypotheses associated with the primary immunogenicity objectives. All analyses are descriptive.

8.4.2.3.2 Analysis Sets

The primary immunogenicity analyses will be based on the per-protocol set (PPS) at Day 29. The primary analyses will be repeated using the Full Analysis Set (FAS) as a measure of the sensitivity/robustness of the results (further details are given in section 8.3).

8.4.2.3.3 Statistical Methods

Before any statistical analysis that assumes normally distributed observations, antibody titers will be $\log_{10}$-transformed. Individual titers below the limit of quantitation (LLQ) will be set to half that limit.

Geometric Mean Titers

The logarithmically (base 10) transformed antibody titers will be modeled using an analysis of covariance (ANCOVA) model with a qualitative factor for LHD153R adjuvant dosage (0 [for unadjuvanted MenC], 12.5, 25, 50 or 100 µg) and log (base 10) pre-vaccination titer as a covariate. The adjusted GMT and the two-sided, 95%, confidence intervals (CIs) of the GMT will be calculated based on this model as will the ratio of GMTs and corresponding CIs. The adjusted GMT and two-sided 95% CIs will be constructed by exponentiation (base 10) of the least square means of the logarithmically transformed (base 10) antibody titer. The ratio of GMTs (LHD153R adjuvant dosage minus Men C), and corresponding two-sided 95% CIs, will be constructed by exponentiation (base 10) of the least square differences obtained from this model. The model can be written as:

$$\log_{10}(y_{ik}) = \mu + \alpha_i + \beta x_{ik} + \varepsilon_{ik}$$

where μ represents a common overall mean, α_i represents the adjuvant dose group i effect, β represents the common slope for the log10 pre-vaccination titer, x_{ik} for subject k in adjuvant dose group I, and ε_{ik} represents random error for subject k in adjuvant dose group i.

Geometric Mean Ratios

The logarithmically (base 10) transformed within subject ratio of antibody titers (Day 29 / pre-vaccination) will be modeled using an analysis of variance model with a qualitative factor for LHD153R adjuvant dosage (0 [for non-LHD153R adjuvanted MenC], 12.5, 25,

50 or 100 µg). The adjusted GMR and the two-sided, 95% CIs of the GMR will be calculated based on this model. The model can be written as:

$\log_{10}(y_{ik}) = \mu + \alpha_i + \varepsilon_{ik}$

where μ represents a common overall mean, α_i represents the adjuvant dose group i effect and ε_{ik} represents random error for subject k in adjuvant dose group i.

Handling of missing values

For immunogenicity data, it may be reasonable to consider missing immunogenicity values as missing completely at random (MCAR), i.e., not informative. Therefore, the primary analysis will comprise a complete case analysis only, without introducing any bias. Imputation methods will not be used.

8.4.3 Analysis of Secondary Objective(s) 8.4.3.1

Analysis of Secondary Safety Objective(s) Not

applicable.

8.4.3.2 Analysis of Secondary Efficacy Objective(s)

Not applicable.

8.4.3.3 Analysis of Secondary Immunogenicity Objective(s)

8.4.3.3.1 Statistical Hypotheses

There are no statistical hypotheses associated with the secondary immunogenicity objectives. All analyses are descriptive.

8.4.3.3.2 Analysis Sets

The secondary immunogenicity analyses will be based on the PPS (further details are given in section 8.3) or the appropriate subset of subjects.

8.4.3.3.3 Statistical Methods

The secondary immunogenicity endpoints are:

- GMTs and corresponding GMRs measured by hSBA directed against MenC for samples collected at Day 8 and Day181.

- Percentage of subjects with hSBA seroresponse at Days 8, 29, and 181. seroresponse is defined as a post vaccination hSBA ≥8 for subjects with a baseline hSBA <4 or have an increase of at least 4 times the baseline hSBA level for subjects with prevaccination hSBA ≥4.
- Antibody geometric mean concentrations (GMCs) against MenC measured by ELISA for samples collected on Days 1 (baseline, prior to vaccination), 8, 29, and 181.
- The percentage of subjects with at least a 4-fold increase in antibody concentrations to MenC as measured by ELISA on Day 8, 29, and 181 relative to baseline (Day 1).

The GMTs for samples collected at Day 8 and Day 181 as well as the GMCs for samples collected at Day 1, Day 8, Day 29, and Day 181 will be analyzed using the same approach as for the primary immunogenicity endpoint.

The remaining immunogenicity endpoints are based on subjects meeting criteria for seroconversion or achieving a certain threshold value. These endpoints will be summarized using frequencies and percentages by LHD153R adjuvant dosage (0 [for non-LHD153R adjuvanted MenC], 12.5, 25, 50 or 100 µg). Two-sided 95% ClopperPearson CIs will also be provided for percentages. For analyses of seroconversion, separate summaries may be provided based on seropositivity status at baseline.

8.4.4 Analysis of Exploratory Objectives

Testing and analyses of exploratory endpoints may be performed after the Clinical Study Report (CSR) has been completed, in which case these data will be submitted as an addendum to the CSR.

In general, concentration and titer results will be summarized for each LHD153R adjuvant dosage group using geometric means and associated 2-sided 95% confidence intervals; and, categorical data will be summarized using frequencies and percentages, with corresponding two-sided, 95% confidence intervals.

8.5 Sample Size and Power Considerations of Primary Objectives

Sample size is not driven by statistical assumptions for formal hypothesis testing, but was based on the safety objective for the study. The table below provides the probability for various combinations of sample size (N) and presumed true frequency of a given event within an individual vaccine group

Frequency of Event	Probability to Observe at Least 1 Subject with a Given Event For Various Choices of N			
	4	**8**	**12**	**16**
0.05	0.1855	0.3366	0.4596	0.5599
0.10	0.3439	0.5695	0.7176	0.8147
0.15	0.4780	0.7275	0.8577	0.9257
0.20	0.5904	0.8322	0.9313	0.9718
0.30	0.8250	0.9423	0.9862	0.9967
0.40	0.8704	0.9832	0.9978	0.9997

The proposed combinations of sample sizes within each cohort are 4 aluminium hydroxide adjuvanted MenC-CRM$_{197}$ and 16 MenC-CRM$_{197}$ plus an assigned-level of LHD153R adsorbed to aluminium hydroxide. If all four cohorts are fully enrolled, there will be 16 subjects receiving aluminium hydroxide adjuvanted MenC-CRM$_{197}$.

With 16 subjects, events which occur at a frequency of 15% or more will be detected with at least 90% probability; and, events which occur at a frequency of 10% or more will be detected with 81% probability. With 4 subjects, events which occur at a frequency of 30% or more will be detected with at least 80% probability. Intermediate values of 8 and 12 are provided to correspond to sample sizes in the MenC- CRM$_{197}$ after cohort 2 and cohort 3 are fully enrolled.

8.6 Interim Analysis

The DMC will be reviewing the accumulating safety data from the study in order to continue enrollment of subjects within a cohort and whether to enroll subjects into the next cohort.

In addition to these periodic reviews, there will be a safety and immunogenicity interim analysis for the selection of an LHD153R adjuvant dosage based on the data collected through Day 29 from subjects enrolled in all cohorts. This analysis will be performed by personnel not involved in study decisions. The results will be unblinded at the group level thereby preserving the blind for individual subjects. No adjustment to the overall alpha will be performed as the data collected subsequent to this analysis involve secondary and exploratory endpoints.

9.0 SOURCE DOCUMENTATION, STUDY MONITORING AND AUDITING

Study monitoring and auditing will be standardized and performed in accordance with the Sponsor's or delegated contract research organization's (CRO) standard operating procedures and applicable regulatory requirements (e.g., FDA, EMA, and ICH guidelines).

Prior to enrolment of the first study subject, Novartis or delegate will train investigators and/or their study staff on the study protocol, all applicable study procedures, documentation practices and all electronic systems. CRFs must be completed for each enrolled subject (see section 8.3.1 for definition of enrolled subject). Documentation of screened but not enrolled subjects must be maintained at the site and made available for review by the site monitor.

9.1 Source Documentation

Prior to the start of the study, the site staff participating in the study conduct will be instructed on what documents will be required for review as source documents. The kinds of documents that will serve as source documents will be agreed between Sponsor or delegate and investigator and designees and specified in the SDA/Source Data Verification Form prior to subject enrolment.

In addition, source documentation **must** include all of the following: subject identification (on each page), eligibility and participation, proper informed consent procedures, dates of visits, adherence to protocol procedures, adequate reporting and follow-up of adverse events, documentation of prior/concomitant medication/vaccines, study vaccine receipt/dispensing/return records, study vaccine administration information, any data collected by a telephone conversation with the subject and date of completion and reason.

The subject must also allow access to the subject's medical records. Each subject must be informed of this prior to the start of the study and consent for access to medical records may be required in accordance with local regulations.

All safety data reported by subjects must be written down in source documents. If there are multiple sources of information (e.g., Subject Diary, verbal report of the subject, telephone contact details, medical chart) supporting the diagnosis of an adverse event, these sources must be identified in the source documents, discrepancies between sources clarified, the ultimate diagnosis must be justified and written in the source documents, and this diagnosis must be captured in the appropriate CRF page. The CRF must also

capture which source(s) of information were used to determine the adverse event (e.g., subject recall, medical chart, Subject Diary).

9.2 Study Monitoring, Auditing and Source Data Verification

Prior to enrolment of the first study subject, Novartis or its designee (e.g., a CRO) will develop a Monitoring Plan to specify how centralized and/or on-site monitoring, including clinical specimens reconciliation, will be performed for the study. Study progress will be monitored as frequently as necessary to ensure:

- that the rights and well-being of human subjects are protected,
- the reported study data are accurate, complete, and verifiable from the source documents and
- the conduct of the study is in compliance with the current approved protocol/amendment(s), GCP and applicable regulatory requirements.

Contact details for the team involved in study monitoring will be provided to the investigator. Study data recorded on CRFs will be verified by checking the CRF entries against source documents in order to ensure data completeness and accuracy as required by study protocol.

Additional documents such as the investigator site file, pharmacy records, and informed consent documentation must also be available for review if requested. Arrangements for monitoring visits will be made in advance in accordance with the monitoring plan, except in case of emergency.

The investigator and/or site staff must make source documents of subjects enrolled in this study available for inspection at the time of each monitoring visit and Sponsor audits, when applicable. These documents must also be available for inspection, verification and copying, as required by regulations, by officials of the regulatory health authorities (e.g., FDA, EMA and others) and/or ECs/IRBs. The investigator and study site staff must comply with applicable privacy, data protection and medical confidentiality laws for use and disclosure of information related to the study and enrolled subjects.

10.0 DATA MANAGEMENT

10.1 Data Entry and Management

In this study, all clinical data (including, but not limited to, AE/SAEs, concomitant medications, medical history, and physical assessments), safety data, and immunogenicity data will be entered into an EDC system, which is compliant with Title 21 Part 11

policies of the Code of Federal Regulations (FDA, 1997). The data system includes password protection and internal quality checks. The EDC system will be designed and validated by the Sponsor prior to activation for data entry by sites. The investigator or designated delegate must review data entered and electronically sign the CRFs to verify their accuracy.

Access to the EDC system for data entry or review will require training and distinct individual access code assignments to those site staff members who will be entering study data and those involved in study oversight who may review study data. Data are collected within the EDC system, to which the Sponsor and site monitors have exclusively "read only" access.

Paper CRFs will be provided for each pregnant subject by the Sponsor. All appropriate pregnant subject data collected will be recorded on this form. One copy must be retained by the investigator, and all other copies (including the original copy) will be returned as directed by the Sponsor. Instructions on how to complete this form will be provided to the investigator.

10.2 Data Clarification

As part of the conduct of the trial, the Sponsor may have questions about the data entered by the site, referred to as queries. The monitors and the Sponsor are the only parties that can generate a query. All corrections and clarifications will be entered into the EDC system and will be identified by the person entering the information, the reason for the change, as well as the time of the changes made. If changes are made to a previously and electronically signed CRF, the investigator must confirm and endorse the changes

10.3 Data Protection

Novartis respects the subjects' rights to privacy and will ensure the confidentiality of their medical information in accordance with all applicable laws and regulations.

The Sponsor as Data Controller according to the European Directive on the protection of individuals with regard to the processing of personal data and on the free movement of such data (95/46/EC) confirms herewith compliance to Directive 95/46/EC in all stages of Data Management.

11.0 RECORD RETENTION

Investigators must retain all study records required by Novartis and by the applicable regulations in a secure and safe facility. The investigator must consult a Novartis representative before disposal of any study records, and must notify the Sponsor of any change in the location, disposition, or custody of the study files. Essential documents must be retained for 15 years. “Essential documents” are defined as documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. These documents should be retained for a longer period, however, if required by the applicable national regulatory or institutional requirements.

These principles of record retention will also be applied to the storage of laboratory samples, provided that the integrity of the stored sample permits testing.

12.0 USE OF INFORMATION AND PUBLICATION

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov, and in compliance with current regulations.

Novartis also assures that key results of this clinical study will be posted in a publicly accessible database within the required time-frame from the End of Study as defined in section 3.9.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Novartis must be notified of any intent to publish data collected from the study and prior approval from Novartis must be obtained prior to submission for publication.

13.0 ETHICS

13.1 Regulatory and Ethical Compliance

The study will be conducted in compliance with the protocol, GCP and applicable regulatory requirement(s).

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, European Directive 2001/20/EC, Novartis codes on protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki (European Council 2001, US Code of Federal Regulations, ICH 1997).

13.2 Informed Consent Procedures

Eligible subjects may only be included in the study after providing written informed consent or assent, as described in section 5.1.1. Before the start of the study, the investigator will have the informed consent and any other materials that will be provided to the subjects reviewed and approved by the IRB/EC. This review and approval will be documented and stored with other study documents. The investigator or designee must fully inform the subject or legal guardian of all pertinent aspects of the study. A copy of the written informed consent will be given to the subject or the designee. The subject/designee must be allowed ample time to ask about the details of the study and to make a decision as to whether or not to participate in the study. The subject and/or legal guardian(s) **must** sign the consent form indicating their agreement to participate in the study before any study-related procedures are conducted. The informed consent process may be conducted up to 23 days prior to vaccination on Day 1. If the subject is unable to read and write, a witness must be present during the informed consent discussion and at the time of informed consent signature.

Prior to the start of the study, Novartis will provide to investigators a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/EC and a copy of the approved version must be provided to Novartis after IRB/EC approval.

Women of childbearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception

requirements indicated in the protocol for the duration of the study. In case of doubt on the ability of a subject to adhere to these requirements, that subject should not be allowed in the study

13.3 Responsibilities of the Investigator and IRB/EC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB/EC before study start. Properly constituted IRB/EC is defined in ICH Guideline for Good Clinical Practice E6 (R1), Section 3 (ICH, 1997). A signed and dated statement that the protocol and informed consent have been approved by the IRB/EC must be given to Novartis before study initiation. Prior to study start and at any time the protocol is amended during study conduct, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/ECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

The investigator also responsible for the following:

- Maintaining a list of appropriately qualified persons to whom the investigator has delegated significant study-related duties.
- Demonstrating the capability of recruiting the required number of suitable subjects within the recruitment period.
- Demonstrating sufficient time and staffing to properly conduct and complete the study within the agreed study period.
- Ensuring that all persons assisting with the study are adequately informed about the protocol, the investigational product(s), and their study-related duties and functions
- Ensuring that appropriately trained health care professionals are responsible for all study-related medical decisions and for ensuring appropriate medical care of subjects experiencing any adverse event related to the study.
- If permission to do so is given by the subject, ensuring that the subject's primary healthcare provider is informed of the subject's participation in the study.

The investigator should not implement any deviation from, or changes of the protocol without agreement by the Sponsor and prior review and documented approval/favourable

opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone number(s)). In addition, the investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to study subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

(a) to the IRB/IEC for review and approval/favourable opinion,

(b) to the Sponsor for agreement and, if required,

(c) to the regulatory authority(ies).

13.4 Protocol Amendments

An amendment is a written description of change(s) to or formal clarification of a study protocol which may impact on the conduct of the clinical study, potential benefit of the clinical study, or may affect subject safety, including changes of study objectives, study design, subject population, sample sizes, study procedures, or significant administrative aspects. An administrative change of a study protocol is a minor correction or clarification that has no significant impact on the way the clinical study is to be conducted and no effect on subject safety (e.g., change of telephone number(s), logistical changes). Protocol amendments must be approved by Novartis, health authorities where required, and the IRB/EC. In cases when the amendment is required in order to protect the subject safety, the amendment can be implemented prior to IRB/EC approval. Notwithstanding, the need for formal approval of a protocol amendment, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action, the IRB/EC at the study site, and, if required by local regulations, the relevant health authority should be informed within 10 working days.

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APPENDIX A: GRADING SCALES FOR SOLICITED LOCAL ADVERSE EVENTS*

(Adapted from CBER 2007b)

Adverse event Following Administration of Injectable Product	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Pain	present but does not interfere with activity	interferes with activity	prevents daily activity
Induration / Swelling / Erythema	25 – 50 mm	51 – 100 mm	> 100 mm

*This toxicity grading scale is adapted from CBER 2007 to enable ease of reporting by Subjects in the source documents for 'patient reported' solicited adverse events. This toxicity grading scale is a Novartis standard that is used for patient reporting. 'Grade 4' is not listed here but will be defined in the Statistical Analysis Plan as necessary.

APPENDIX B: GRADING SCALES FOR SOLICITED SYSTEMIC ADVERSE EVENTS*

(Adapted from CBER 2007b)

Systemic Adverse event		Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Fever	**°C**	38.0 – 38.4	38.5 – 38.9	39.0 – 40
	°F	100.4 – 101.1	101.2 - 102	102.1 - 104
Chills		present but does not interfere with activity	interferes with activity	prevents daily activity
Loss of Appetite		Loss of appetite without decreased oral intake	decreased oral intake without weight loss	decreased oral intake with weight loss
Nausea		Nausea present but not interfering with oral intake	Nausea leading to decreased oral intake	Nausea leading to minimal to no oral intake
Vomiting		1-2 episodes/24 hours	>2 episodes/24 hours	requires outpatient hydratation
Diarrhea		2-3 loose stools /24 hours	4-5 loose stools /24 hours	6 or more watery stools /24 hours or requires outpatient IV hydration
Generalized Myalgia		present but does not interfere with activity	interferes with activity	prevents daily activity
Generalized Arthralgia		present but does not interfere with activity	interferes with activity	prevents daily activity
Headache		present but does not interfere with activity	interferes with activity	prevents daily activity
Fatigue		present but does not interfere with activity	interferes with activity	prevents daily activity
Generalized Rash		localized area of the skin (1 extremity only)	moderate area of the skin (2 or more body regions without whole body involvement)	most of the skin
Urticaria		localized area of the skin (1 extremity only)	moderate area of the skin (2 or more body regions without whole body involvement)	most of the skin

*This toxicity grading scale is adapted from CBER 2007b to enable ease of reporting by Subjects in the source documents for 'patient reported' solicited adverse events. This toxicity grading scale is a Novartis

standard that is used for patient reporting. ‘Grade 4’ is not listed here but will be defined in the statistical analysis plan as necessary

APPENDIX C: TOXICITY SCALES FOR LABORATORY ABNORMALITIES (SERUM CLINICAL CHEMISTRY)

Serum*,**	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)***
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN

*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

TOXICITY SCALES FOR LABORATORY ABNORMALITIES

**Laboratory values that fall in the normal range may be assigned a category of "Grade 0."

***The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value. "ULN" = the upper limit of the normal range.

APPENDIX D:

(HEMATOLOGY)

Hematology*,*	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000

TOXICITY SCALES FOR LABORATORY ABNORMALITIES

Platelets Decreased cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000

*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

**Laboratory values that fall in the normal range may be assigned a category of "Grade 0."

APPENDIX E:

(URINE)

Urine*,**	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

**Laboratory values that fall in the normal range may be assigned a category of "Grade 0."

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Document Approval Certificate /

PPD

The individuals listed have approved this document for implementation using an electronic signature in the
Atlas EDMS. PPD

UserName: PPD Title: Cluster Physician Date: Thursday, 11 September 2014, 08:53 GMT
Meaning: As an approver, I agree with the content and format of this document.

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CLINICAL STUDY PROTOCOL SPONSOR SIGNATURE PAGE

Study Number: V132_01EXP

Protocol Title: A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine in Healthy Adults (18-45 years of age)

Date of Final Issued Protocol and Version: 10 SEP 14, Version 2

Signature page for sponsor's representative

The following sponsor's representative has reviewed and approved the protocol entitled "A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine in Healthy Adults (18-45 years of age)." In addition, this study protocol has been approved by the Novartis Vaccines and Diagnostics Protocol Review Committee and received an electronic approval signature on 11 Sep 14.

[redacted]

…….. 27/OCT/14

Cluster Physician, Novartis Vaccines and Diagnostics — Date, DD MMM YY

[redacted]

Printed Name of Cluster Physician, Novartis Vaccines and Diagnostics

PPD

CLINICAL STUDY PROTOCOL AMENDMENT

Study Number: V132_01EXP

Protocol Title: A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine in Healthy Adults (18-45 years of age)

Amendment Number 2

Revised Protocol version 3.0 issued on 17 DEC 2014

The present amendment reflects changes to the Protocol version 2.0 issued on 10SEP14

DESCRIPTION OF CHANGE(S) AND RATIONALE:

CHANGE	LOCATION(S) OF CHANGE	RATIONALE FOR CHANGE
Escalation of the LHD153 dosage will be based on DMC review of Day 14 safety results of the first 5 subjects in the previous dosage cohort. Furthermore, all available Day 14 and Day 29 safety results will be included in DMC reviews between the different enrollment stages. Previously escalation to the next dosage was based on DMC review of Day 29 safety data of the entire previous dosage cohort.	Synopsis, Study Design (Page 11; Table 2) Synopsis, Data Monitoring Committee (Page 18-19) Section 3.1 'Study Design' (Page 32; Table 3.1-2) Section 3.7 'Data Monitoring Committee' (Page 38)	Opportunity to reduce the enrollment period by reducing the number of DMC reviews without impact on subject safety (i.e. no change in enrollment rate of first 5 subjects, no change in criteria of enrollment of the remaining 15 subjects in each cohort, no change in the safety assessments, no change in stopping rules).
Deletion of 'complement fixing capacity' from the list of prioritized antibody functionality assessments as part of Exploratory Endpoint #4.	Synopsis, Exploratory Endpoint #4, Page 17 Section 7.4 'Exploratory Measurements' (Page 74) Section 8.1.3 'Exploratory Endpoints' (Page 76)	Antibody functionality assessments as part of Exploratory Endpoints will be performed on serum samples that are left-over from the primary and secondary immunogenicity end-point assessments. "Complement fixing capacity" has been deleted from the list of prioritized assessments as it is not essential for determining the antibody functionality and we may experience limited quantity of serum available for this analysis.

Novartis

Document Approval Certificate /

PPD

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Atlas EDMS PPD

UserName: PPD Title: Cluster Physician Date: Wednesday, 17 December 2014, 14:49 GMT
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CLINICAL STUDY PROTOCOL V132_01EXP Version 3

A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine in Healthy Adults (18-45 years of age)

EUDRACT No. 2014-002430-31

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PROTOCOL SYNOPSIS V132_01EXP

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
Novartis Pharma Services AG	V132_01EXP	MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and Meningococcal C-CRM$_{197}$ Conjugate Vaccine
Title of Study: A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine in Healthy Adults (18-45 years of age)		
Study Period: Approximately 12 months for each subject		**Clinical Phase:** Phase 1

Background and Rationale:

Neisseria meningitidis (*N. meningitides*)serogroup C (MenC) is one of the major serogroups causing invasive meningococcal disease. Case fatality in Germany has ranged between 6% and 8% between 1999 and 2006, and has remained generally consistent across the different European countries, varying between 6-11%, with the case fatality rate being notably higher for serogroup C disease than for serogroup B. The safety and immunogenicity of the Novartis Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) has been confirmed through years of commercial use. For children over the age of 12 months, for adolescents and for adults a single dose is recommended. For infants between 2 and 12 months of age, the recommended schedule for primary immunization with the Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) is two doses given with an interval of at least 2 months (Novartis Meningococcal C-CRM$_{197}$ Conjugate Vaccine Investigator Brochure).

A more potent Meningococcal C-CRM$_{197}$ Conjugate Vaccine formulation might enable a reduction of the antigen dosage and/or a reduction in the number of doses needed in infants. One approach to achieve more potent well-characterized sub-unit vaccines - like the Novartis Meningococcal C-CRM$_{197}$ Conjugate Vaccine - is the use of new adjuvants that activate the Toll-like receptor (TLR) pathway.

Novartis is developing a small molecule immune potentiator (SMIP) LHD153 that is an agonist for TLR7. The objective driving the development of LHD153 is to achieve a vaccine adjuvant with strong immunopotentiating properties and minimal side effects. In

line with this objective, it has been postulated that the ideal SMIP should remain local and target innate immune cells at the injection site. To this end, LHD153 contains a

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
Novartis Pharma Services AG	V132_01EXP	MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and Meningococcal C-CRM$_{197}$ Conjugate Vaccine

functional phosphonate group to allow for adsorption to aluminium hydroxide. The arginine salt derivative of this compound is LHD153R. Preclinical results from animal models for bacterial and viral antigens, including MenC, MenB, rabies, HIV and respiratory syncytial virus (RSV) showed increased functional antibodies and antigenspecific T-cells with LHD153R adsorbed to aluminium hydroxide (Aluminium Hydroxide/LHD153R) when compared to aluminium hydroxide adjuvanted controls. *In vitro* toxicity screens confirmed that LHD153R is not phototoxic, genotoxic or mutagenic. Furthermore, toxicology studies in dog and rats showed that intramuscular (IM) injection of Aluminium Hydroxide/LHD153R was well tolerated. Importantly, in contrast to free LHD153R, toxicokinetic analysis in rats and dogs confirmed very limited exposure of LHD153 when LHD153R was adsorbed to aluminium hydroxide after IM injection.

The aim of this Phase 1 clinical study is to assess the safety of Aluminium Hydroxide/LHD153R adjuvanted MenC-CRM_{197} conjugate vaccine (MenCCRM$_{197}$/Aluminium Hydroxide/LHD153R) and to compare the antibody-mediated immune response elicited by MenC-CRM_{197}/Aluminium Hydroxide/LHD153R with the licensed aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (Menjugate®). Furthermore, a comprehensive set of exploratory objectives has been selected to assess the systemic exposure of LHD153 after intramuscular injection of MenC-CRM_{197}/Aluminium Hydroxide/LHD153R, to evaluate the quality of the specific immune response against MenC-CRM_{197} in detail and to evaluate biomarkers that may be predictive of safety and/or innate immune activation.

The licensed Meningococcal C-CRM_{197} Conjugate Vaccine (Menjugate®) has been selected as the primary vaccine candidate to assess the safety and immunopotentiating properties of Aluminium Hydroxide/LHD153R for several reasons. Firstly, the safety and immunogenicity profiles of the Meningococcal C-CRM_{197} Conjugate Vaccine (Menjugate®) have been well established through years of commercial use. Secondly, a more potent MenC-CRM_{197} conjugate vaccine might enable a reduction of the antigen dosage or the number of doses needed in infants. Finally, the MenC-CRM_{197} conjugate is a well-characterized, single antigen preparation which provides an ideal setting to evaluate the potential of this new Aluminium Hydroxide/LHD153R adjuvant.

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Study Objectives:

Primary Safety Objective:

To assess the safety of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R as compared to that of aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine.

Primary Immunogenicity Objective:

To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine at Day 29, as measured by human complement serum bactericidal assay (hSBA) directed against MenC.

Secondary Immunogenicity Objectives:

1. To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal CCRM$_{197}$ Conjugate Vaccine, at Day 8 and Day 181 after vaccination, as measured by hSBA directed against MenC. Baseline antibody titers will also be measured by hSBA.
2. To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal CCRM$_{197}$ Conjugate Vaccine at Day 8, Day 29 and Day 181 after vaccination, as measured by an enzyme-linked immunosorbent assay (ELISA) to MenC. Baseline antibody concentrations will also be measured by ELISA.

Exploratory Objectives:

1. To evaluate the systemic exposure of LHD153 at several early time-points after IM injection of MenC-CRM197/Aluminium Hydroxide/LHD153R or aluminium hydroxide adjuvanted Meningococcal C-CRM197 Conjugate Vaccine.
2. To explore the frequency of B cells specific for MenC polysaccharide and CRM$_{197}$ protein at baseline (Day 1) and at Day 8, Day 29 and Day 181 after vaccination with

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MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R or the aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine. Subsequently, the B cell repertoire of the antigen specific B cells and the specific antibody functionality will be analyzed in a selected subset of subjects.

3. To explore the baseline T cell mediated immunity to CRM$_{197}$ and to evaluate the frequency and quality of CRM$_{197}$ specific T cells induced by MenC-CRM$_{197}$/Aluminium Hydroxide/ LHD153R compared to aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine at Day 8 and Day 29.
4. To evaluate biomarkers that may be predictive for safety and/or innate immune activation.

Study Design:

This Phase 1, randomized, observer-blind, dosage-escalation study will be performed at a single center. In total, approximately 80 healthy male and healthy non-pregnant female adults (18-45 years of age) will be enrolled in the study. Subjects will be randomized to receive a single IM vaccination of either the licensed aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine (i.e. 10 µg MenC conjugated to CRM$_{197}$, adjuvanted with 1 mg aluminium hydroxide) or one of four dosages of the investigational vaccine, MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R (i.e. 10 µg MenC conjugated to CRM$_{197,}$ adjuvanted with 1 mg aluminium hydroxide and one of four dosages [12.5, 25, 50 or 100 µg] of LHD153R).

For the dosage-escalation of LHD153R, the subjects will be enrolled into 1 of 4 cohorts, in a stepwise manner with 20 subjects per cohort. Subjects in all cohorts will be randomized in a 1:4 ratio, to receive either aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine (control) or MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R with increasing doses of LHD153R.Cohort 1 will receive 12.5 µg of LHD153R; Cohort 2 will receive 25 µg of LHD153R; Cohort 3 will receive 50 µg of LHD 153; and Cohort 4 will receive 100 µg of LHD153R (Table 1).

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Table 1. Subjects Randomized per Cohort and Treatment Dose Group

Cohort	Group	Subjects/ Group	MenC Dosage* (µg)	Adjuvant Dosages		Total Volume/Dose	Total Subjects/Group
				Aluminium Hydroxide (mg)	LHD153R (µg)		
1	A	4	10	1	0	0.5 mL	20
	B	16	10	1	12.5	0.5 mL	
2	A	4	10	1	0	0.5 mL	20
	C	16	10	1	25	0.5 mL	
3	A	4	10	1	0	0.5 mL	20
	D	16	10	1	50	0.5 mL	
4	A	4	10	1	0	0.5 mL	20
	E	16	10	1	100	0.5 mL	

*Conjugated to 12.5-25 µg CRM_{197}

After vaccination, all subjects will be confined to the clinical site for 24 hours for clinical observation, including but not limited to observations for solicited and unsolicited adverse events, body temperature measurements and blood sampling for exploratory endpoint measurements.

Importantly, all cohorts will have a staggered entry based on Data Monitoring Committee (DMC) reviews.

- For each cohort, the first 5 subjects (i.e. the first 1:4 randomization block) to receive either aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (n=1) or MenC-CRM_{197}/Aluminium Hydroxide/LHD153R (n=4) will be treated at a vaccination rate of 1 subject each day.
- After entry of the first 5 subjects in each cohort, the enrollment will be paused. The remaining 15 subjects for each cohort will be enrolled only after DMC review of the safety results obtained through Day 14 has been finalized (Table 2).
- In addition, enrollment of the first 5 subjects in the next cohort will only proceed after the Day 14 safety results of the first 5 subjects of the previous cohort have been reviewed by the DMC (Table 2).

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- Furthermore, all available Day 14 and Day 29 safety results will be included in DMC reviews between the different enrollment stages.

Table 2. Overview of staggered entry of subjects based on DMC reviews

Stage	Dosage Cohort	MenC-CRM$_{197}$/ Aluminium Hydroxide (n)	MenC-CRM$_{197}$/ Aluminium Hydroxide /LHD153R (n)
1	1	1	4
Enrollment pause until DMC review of Stage 1 Day 14 Safety Results			
2	1	3	12
	2	1	4
Enrollment pause until DMC review of Stage 1 Day 29 and Stage 2 Day 14 Safety Results			
3	2	3	12
	3	1	4
Enrollment pause until DMC review of Stage 2 Day 29 and Stage 3 Day 14 Safety Results			
4	3	3	12
	4	1	4
Enrollment pause until DMC review of Stage 3 Day 29 and Stage 4 Day 14 Safety Results			
5	4	3	12

The DMC review will be performed according to predefined stopping/pausing guidelines used to ensure the safety of study subjects. These stopping/pausing guidelines are based on FDA guidance and with grading scales from the CBER Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials". See protocol section 3.6 for further details.

Safety Measurements

Schedule of safety data collection:

- Solicited local and systemic adverse events (AEs), body temperature and all unsolicited AEs will be collected until Day 14.
- All serious adverse events (SAEs), medically attended AEs, AEs leading to study withdrawal, new onset of chronic disease (NOCDs), and adverse events of special

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interest (AESIs) will be collected from the date of signed informed consent to study completion at Day 366.

- All concomitant medications administered in relation to the reported AEs will be collected from vaccination to study completion at Day 366.

Solicited local AEs include injection site erythema, injection site induration, injection site pain and injection site swelling. Solicited systemic AEs include body temperature ≥ 38.0°C (as measured orally), loss of appetite, nausea, fatigue, generalized myalgia, generalized arthralgia, headache, chills, vomiting, diarrhea, generalized rash and urticaria.

All AESIs will be reported in the same manner as SAEs. All AEs will be monitored until resolution or, if the AE becomes chronic, a cause is identified. If an AE is unresolved at the conclusion of the study, a clinical assessment will be made by the investigator and the medical monitor to determine whether or not continued follow-up of the AE is warranted.

The relationship of the study treatment to any AE will be determined by the investigator as probably related, possibly related, or not related; the relationship of the study treatment to any SAE will be determined by the investigator as probably related/suspected, or not related.

Safety Laboratory Parameters

To assess laboratory AEs, blood and urine samples will be collected from each subject as outlined in Table 3 to perform blood chemistry, hematology, and urine analyses.

Safety laboratory samples will be drawn from all subjects at pre-vaccination screening (between Day -28 and Day -3) at Day 1 (pre-vaccination), at Day 8 and at Day 29. Safety laboratory assessments will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, liver function tests (ALT, AST), a complete blood count and C-reactive protein. A urine sample will be collected at the same time-points and will be assessed for the presence of protein, glucose and red blood cells.

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Primary and Secondary Immunogenicity Measurements

Four blood samples per subject (i.e. at Day 1, Day 8, Day 29 and Day 181) will be collected for serum preparation and determination of antibody-mediated immune responses to MenC-CRM$_{197}$ as outlined in Table 3 and Table 4. See section 7.3 for further details.

Exploratory Measurements

In all subjects who agree by signing a separate Informed Consent, additional blood samples will be collected at Day 1, Day 4, Day 8, Day 29 and Day 181 for exploratory assays as outlined in Table 3 and Table 4. The purpose of these assays is to assess the systemic exposure of LHD153, to determine the frequency and quality of B- and T-cells specific for MenC polysaccharide and/or CRM$_{197}$ and to evaluate biomarkers that may be predictive of safety and/or innate immune activation. Subsequently, MenC-CRM$_{197}$ specific B-cell repertoires as well as the MenC-CRM$_{197}$ specific antibody functionalities will be analyzed in a selected subset of subjects, dependent on the results from primary and secondary immunogenicity measurements and the volume of whole blood (specific B cell repertoire) and serum (specific antibody functionality) remaining for additional testing. See section 7.4 for further details. All exploratory analyses may be performed after the Clinical Study Report (CSR) has been completed, in which case these data will be submitted as an addendum to the CSR.

Number of Subjects planned:

Approximately 80 adult subjects will be randomized, with anticipated dropout rates of 5% by Day 181 (last serology time point), and 10%, by Day 366 (last safety time point).

Sample size is not driven by statistical assumptions for formal hypothesis testing, but the proposed number of subjects will be sufficient to provide a descriptive summary of the safety and immunogenicity of the study vaccine.

Study Population and Subject Characteristics:

Healthy adult male and female volunteers between 18-45 years of age, inclusive.

The list of inclusion and exclusion criteria is included in protocol section 4.0.

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Study Vaccines:

The MenC-CRM$_{197}$ conjugate is a lyophilized powder consisting of 10 µg of MenC polysaccharide conjugated to 12.5-25 µg CRM$_{197}$ carrier protein. The MenC-CRM$_{197}$ lyophilized powder will be reconstituted with adjuvant by the unblinded designated site staff member who is to follow the procedure as described in the vaccine preparation instructions in the Investigator Site File (i.e. the vaccine will be prepared in the clinic prior to administration).

The lyophilized MenC-CRM$_{197}$ powder will be reconstituted with either:

(a) aluminium hydroxide adjuvant

(b) Aluminium Hydroxide/LHD153R adjuvant with specified dosages of LHD153R (12.5, 25, 50 or 100 µg)

The components for each formulation of MenC-CRM$_{197}$ will be provided in a separate kit.

Aluminium Hydroxide/LHD153R with specified dosages of LHD153R will be prepared by dilution of the highest Aluminium Hydroxide/LHD153R dosage (100 µg of LHD153R) with aluminium hydroxide.

In each cohort, subjects will be randomized to receive one injection of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R adjuvant or aluminium hydroxide adjuvanted

Meningococcal C-CRM$_{197}$ Conjugate Vaccine. The 0.5 mL of vaccine will be injected IM in the deltoid muscle, with preference that the injection is administered in the nondominant arm.
Primary Safety Endpoint: Safety will be assessed by measuring the frequency of local and systemic solicited AEs, unsolicited AEs, SAEs, AESIs, NOCDs, and safety laboratory data for all subjects. Specifically, ▫ The frequency and percentage of subjects with solicited local and systemic AEs through Day 14. Time intervals after vaccination that will be summarized are: 30 min post-vaccination, Days 1-4 (without 30 min), Days 5-8, Days 8-14, Days 1-8

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(without 30 min) and Days 1-14 (without 30 min).

- The frequency and percentage of subjects with any unsolicited AEs from the day of vaccination (Day 1) to Day 14.
- The frequency and percentage of subjects with SAEs, medically attended AEs, AEs leading to study withdrawal, NOCDs, AESIs for the following time periods: day of signed informed consent until study completion (Day 366), day of vaccination (Day 1) to Day 29 and Day 29 to study completion (Day 366).
- The absolute values and changes in hematology, chemistry, and urinalysis parameters.
- The frequency and percentage of subjects with abnormal laboratory parameter values as classified by investigator normal ranges (low, normal, high) and as classified by CBER toxicity grading scales, when available.

Primary Immunogenicity Endpoint:

Geometric mean titers (GMTs) measured by hSBA directed against MenC from samples collected on Day 1 (baseline, before vaccination) and Day 29 as well as the GMR of the titers (Day 29 / Day 1).

Secondary Immunogenicity Endpoints:

- GMTs and corresponding GMRs measured by hSBA directed against MenC for samples collected at Day 8 and Day181.
- Percentage of subjects with hSBA seroresponse at Day 8, Day 29, and Day 181. seroresponse is defined as a post vaccination hSBA $\geq$8 for subjects with a baseline hSBA <4 or have an increase of at least 4 times the baseline hSBA level for subjects with pre-vaccination hSBA $\geq$4.
- Antibody geometric mean concentrations (GMCs) against MenC measured by ELISA for samples collected on Day 1 (baseline, prior to vaccination), Day 8, Day 29, and Day 181.
- The percentage of subjects with at least a 4-fold increase in antibody concentrations to MenC measured by ELISA on Day 8, Day 29, and Day 181 relative to baseline

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(Day 1).

Exploratory Endpoints:

Testing and analyses of exploratory endpoints may be performed after the Clinical Study Report (CSR) has been completed, in which case these data will be submitted as an addendum to the CSR.

1. Serum concentration of LHD153 at Day 1 baseline (prior to vaccination), Day 1 (1h , 2h, 4h, 8h, and 24h after vaccination) and Day 4 by LC-MS/MS.
2. Frequency of MenC polysaccharide-specific and CRM$_{197}$-specific B cells at Day 1 (baseline), Day 8, Day 29, and Day 181 by ELISPOT.
3. Diversity of the MenC polysaccharide-specific B-cell repertoire at Day 1 (baseline), Day 8, Day 29, and Day 181 by immunoglobulin cDNA sequencing.
4. Functionality of antigen specific antibodies will be assessed at Day 1 (baseline), Day 8, Day 29, and Day 181 by analysis of immunoglobulin isotype, glycosylation state and their ability to fix complement, to promote antibody-dependent cell mediated cytoxicity, to induce phagocytosis and to activate FcR+ cells. If the quantity of serum available for this specific exploratory objective is limited, assessments of immunoglobulin isotype and glycosylation state will be prioritized over the other assessments.
5. Frequency and quality of T cells specific for CRM$_{197}$ at Day 1 (baseline), Day 8, and Day 29 by fluorescence activated cell sorting (FACS) analysis using intracellular staining with a panel of cytokines and surface markers to identify cell populations.
6. Serum concentrations of a panel of 30 chemokines and cytokines at Day 1 baseline (prior to vaccination), Day 1 (6h and 24h after vaccination), Day 4, and Day 8 by electrochemo-luminescence based assay.
7. Gene expression profile in whole blood at Day 1 baseline (prior to vaccination), Day 1 (6h and 24h after vaccination), Day 4, and Day 8 by RNA micro array analysis.

Statistical Analyses:
The study is exploratory in nature, thus analyses will be descriptive and no formal hypothesis testing will be performed. Primary Safety Analyses The primary safety analyses will be based on the safety set for solicited and unsolicited adverse events. There is no statistical null hypothesis associated with the safety objective, which will be analyzed descriptively. Immunogenicity Analyses The primary immunogenicity analyses will be based on the per-protocol set (PPS) on Day 29. The primary analyses will also be performed using the Full Analysis Set (FAS) as a measure of the sensitivity/robustness of the results. All other immunogenicity assessments will be performed using the PPS or the appropriate subset of subjects. The antibody concentrations/titers will be summarized using GMC/GMTs and two-sided 95% confidence intervals (CIs) constructed by exponentiation (base 10) of the least square means of the logarithmically transformed (base 10) antibody titer. The 95% CIs will be obtained from an analysis of covariance (ANCOVA) with baseline concentration/titer as a covariate. Additional details will be further described in the Statistical Analysis Plan. The immunogenicity endpoints based on subjects meeting criteria for seroconversion or achieving a certain threshold value will be summarized using frequencies and percentages and associated two-sided 95% Clopper-Pearson CIs. For analyses of seroconversion, separate summaries may be provided based on seropositivity status at baseline.

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Interim Analysis: An Interim Analysis will be performed on the immunogenicity and safety data collected from all subjects until Day 29, after all cohorts have been enrolled. Further details regarding the interim analysis are contained in section 8.6.
Data Monitoring Committee: A DMC will be implemented to review safety data during scheduled periodic reviews.

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The DMC will review safety data collected until Day 14, as described in the DMC charter and in the Statistical Analysis Plan, after enrollment of the first 5 subjects in each cohort, before proceeding with enrollment of the remaining 15 subjects in each cohort. In addition, enrollment of the first 5 subjects of the next cohort will only proceed after the Day 14 safety results of the first 5 subjects of the previous cohort have been reviewed. Furthermore, all available Day 14 and Day 29 safety results will be included in DMC reviews between the different enrollment stages. Further information regarding the DMC is discussed in more detail in the protocol, section 3.7.		

Table 3: Time and Events Table – Treatment Period (until Day 29)

	Visit Type	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Phone Call**	**Clinic Visit**
	Study Day	**-28 to -3**	**1**	**4**	**8**	**15**	**22**	**29**
	Visit Window (Days)	**n/a**	**n/a**	**n/a**	**-1/+1**	**+1**	**n/a**	**-2/+2**
	Visit Number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**
Study Event	**References**							
Study Treatment								
Vaccination	Section 5.2		X					
Screening and Safety								
Informed Consent	Section 5.1.1	X						
Demographic Data & Medical History	Sections 5.1.2	X						
Physical Exam	Sections 5.1.2 and 5.2.1	X	X[a]					
Safety Laboratory blood draw (10 ml)	Section 7.1.7	X	X[a]		X			X
Urinalysis	Sections 7.1.7	X	X[a]		X			X
Pregnancy Test	Sections 5.1.2 and 5.2.1	X	X[a]					
Exclusion/Inclusion Criteria	Section 4.0	X	X[a]					
Randomization	Section 5.2.3		X[a]					
30 min and 24 hr Post Injection Assessment	Section 5.2.5		X[b]					
Subject Diary Dispensed with Training	Section 5.2.5		X					
Subject Diary Reminder	Section 5.2.5			X	X			

Subject Diary Reviewed and Collected	Section 5.3.1					X		
Assess all solicited AEs	Section 7.1.1 and 7.1.3					X		
Assess all unsolicited AEs	Sections 7.1.2 and 7.1.3	X	X	X	X	X		

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	Visit Type	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Phone Call**	**Clinic Visit**
	Study Day	**-28 to -3**	**1**	**4**	**8**	**15**	**22**	**29**
	Visit Window (Days)	**n/a**	**n/a**	**n/a**	**-1/+1**	**+1**	**n/a**	**-2/+2**
	Visit Number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**
Study Event	**References**							
Assess SAEs	Section 7.1.4	X	X	X	X	X	X	X
Assess AESIs	Section 7.1.4.1	X	X	X	X	X	X	X
Assess NOCDs, medically attended AEs, AEs leading to withdrawal	Sections 7.1.3	X	X	X	X	X	X	X
Assess relevant medications	Sections 5.1.2 and 6.5	X	X	X	X	X	X	X
Blood draws for Immunogenicity and Exploratory Objectives								
Serum Blood Draw (Primary and Secondary Objectives; 10 mL)	Section 3.5		X_a		X			X
Serum Blood Draw (Exploratory Objectives; 5 mL)	Section 3.5		X_c	X	X			
Whole Blood Draws (Exploratory Objectives; 2 mL)	Section 3.5		X_d	X				
Whole Blood Draw (Exploratory Objectives; 5 mL)	Section 3.5		X_e	X	X			

Whole Blood Draw (Exploratory Objectives; 50 mL)	Section 3.5		X_a		X			X

Notes:
a. Procedure must be performed prior to vaccination.
b. Body temperature measurement must be performed at 30 min, 2, 4, 6, 8, 10, 12, 20 and 24 hours after vaccination.
c. Three Serum Blood Draws (3 x 5ml) must be taken at Study Day 1, i.e. at baseline (prior to vaccination), at 6h and at 24h after vaccination.
d. Six whole Blood Draws (6 x 2 mL) must be taken at Study Day 1, i.e. at baseline (prior to vaccination) and at 1, 2, 4, 8 and 24h after vaccination.
e. Three Whole Blood Draw (3 x 5 mL) must be taken at Study Day 1, i.e. at baseline (prior to vaccination), at 6h and at 24h after vaccination

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Table 4: Time and Events Table – Follow-up Period (until Day 366)

	Visit Type	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Phone Call**	**Phone Call**	**Clinic Visit**
	Study Day	**85**	**113**	**181**	**209**	**271**	**366**
	Visit Window (Days)	**-7 to +7**	**-7 to +7**	**-7 to +7**	**-14 to +14**	**-14 to +14**	**-14 to +14**
	Visit Number	**7**	**8**	**9**	**10**	**11**	**12**
Study Event	**References**						
Safety							
Assess SAEs	Section 7.1.4	X	X	X	X	X	X
Assess AESI	Section 7.1.4.1	X	X	X	X	X	X
Assess NOCDs, medically attended AEs, AEs leading to withdrawal	Sections 7.1.3	X	X	X	X	X	X
Assess relevant medications	Sections 5.1.2 and 6.5	X	X	X	X	X	X
Blood draws for Immunogenicity and Exploratory Objectives							
Serum Blood Draw (Secondary Objective; 10 mL)	Section 3.5			X			

Whole Blood Draw (Exploratory Objectives; 50 mL)	Section 3.5			X			
Study Completion Procedures							
Study Termination[a]	Section 5.5						X

Notes:
a. Subjects who terminate the study early are recommended to complete certain study-related procedures. See section 5.5 for further details.

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LIST OF ABBREVIATIONS

ADCC	Antibody-dependent cell mediated cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BZN	Benzonaphthyridines
CBER	Center for Biologics Evaluation and Research
cDNA	Complementary deoxyribonucleic acid
CI	Confidence interval
CRF	Case report form
CRM_{197}	Cross Reacting Material 197
CSR	Clinical Study Report
DMC	Data Monitoring Committee
EC	Ethics committee
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
ELISPOT	Enzyme-Linked ImmunoSpot
EMA	European Medicines Agency
FACS	Fluorescence-activated cell sorting
FAS	Full analysis set
FDA	Federal Drug Agency
GCP	Good clinical practice
GMC	Geometric mean concentration
GMP	Good manufacturing practice

GMT	Geometric mean titer
GMR	Geometric mean ratio
HEENT	Head, ears, eyes, nose and throat
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
hSBA	Human complement serum bactericidal assay
ICF	Informed consent form
ICH	International Committee for Harmonization
IM	Intramuscular
IRB	Institutional review board
IV	Intravenous
LLQ	Lower limit of quantification
MenC	Meningococcal type C
MPL	Monophosphoryl lipid A
NCR	No carbon required
NOCD	New Onset of Chronic Disease
PEG	Polyethylene glycol
PO	Per oral
PP	Per protocol
RNA	Ribonucleic acid (RNA
SAE	Serious Adverse Event
SMIP	Small molecule immune potentiator
TLR	Toll-like receptor
VSAE	Vaccine serious adverse event

1.0 BACKGROUND AND RATIONALE

1.1 Background

MenC-CRM$_{197}$ Conjugate Vaccine

Meningococcal disease worldwide is predominantly a disease of infants and young children. *N. meningitidis* serogroup B and C remain the most prevalent strains in North America and Europe, (Rosenstein, N. et al., 2001) and together cause more than 95% of reported cases of meningococcal disease in Europe (Connolly, M, et al., 1999). In Europe, *N. meningitidis* serogroup C (MenC) is one of the major serogroups causing invasive disease. Case fatality in Germany has ranged between 6% and 8% between 1999 and 2006, and has remained generally consistent across the different European countries, varying between 6-11%, with the case fatality rate being notably higher for serogroup C disease than for serogroup B (European Centre for Disease Prevention and Control, 2011). Since MenC vaccination was added to Germany's routine schedule for children in 2006, there has been a reported decline in MenC incidence. However, the decline was not as rapid when compared to other European countries (Hellenbrand, W. et al., 2013).

The Novartis Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) comprises MenC oligosaccharides conjugated to the protein carrier, CRM$_{197}$, a nontoxic mutant of diphtheria toxin. The vaccine has been shown to be safe and immunogenic and able to prime infants, toddlers and young children for immunological memory (see Novartis Meningococcal C-CRM$_{197}$ Conjugate Vaccine Investigator's Brochure).

In Germany, the Standing Committee on Vaccination (STIKO) of the Robert Koch Institute recommends a single dose of MenC conjugate vaccine in children over the age of 12 months as part of the routine vaccination campaign (Robert Koch Institute Epidemiologisches Bulletin, August 2013). For specific indications, e.g. in case of postexposure prophylaxis, the recommended schedule for primary immunization of infants between 2 to 12 months of age with a MenC conjugate vaccine is two dosages given with an interval of at least 2 months.

Although the Novartis Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) represents an example of how vaccination with a well characterized, purified polysaccharide antigen can yield pivotal public health triumphs, there remains a need for further improvement of the MenC vaccine. A more potent MenC vaccine formulation might yield an increase in the magnitude of the antigen-specific immune response enabling a reduction of the antigen dosage. Furthermore, induction of a more rapid antigen-specific immune response may enable a reduction in the number of doses needed for post-exposure prophylaxis in infants.

Vaccine Adjuvants

Immunization with purified protein or polysaccharide antigens typically results in the induction of a modest antibody response with little or no T cell response when compared to vaccines comprised of whole or killed bacteria or viruses that have inherent immunepotentiating activity. The need to increase the immunogenic response of wellcharacterized and purified antigens that display suboptimal immunogenicity when used alone affirms the essential role for the use of adjuvants. Vaccine adjuvants may significantly reduce the amount of antigen needed (Del Giudice, G, et al., 2013) and may induce a more rapid immune response enabling a reduction in the number of doses in a regimen.

Besides reducing the antigen dosage or number of doses in the vaccine regimen, there is now an increased appreciation of the capacity of adjuvants to increase not just overall antibody titer but also to increase the number of functional antibodies and/or antibodies with higher affinity for vaccine antigens. Many pathogens, such as influenza viruses, HIV, human papilloma virus (HPV) and the malaria parasite, display substantial antigenic drift, subtype and/or strain variations. Therefore, the ability of adjuvants to broaden an immune response profile could be crucial to the success of vaccines against such targets. Previous studies have shown that the broadening effect of adjuvants may be mediated via expansion of B cell diversity, not merely through increased titers (Khurana, et al., 2010, 2011). Clinically, antibody response broadening by adjuvants such as AS04 or oil-inwater emulsions has been demonstrated in HPV vaccines and influenza, respectively (Bissett, SL et al., 2014; Del Giudice, G et al., 2013).

One unmet need is the development of vaccines for effective T cell responses. Several vaccines in development are aimed at eliciting T cell responses, which historically have not been induced by the most commonly used adjuvants in vaccines for human use, such as aluminium hydroxide. Therefore, an objective of many adjuvant discovery and development programs is to elicit more effective engagement of T-helper cells for optimizing the quality, breadth and durability of antibody responses, or, to induce effector CD4+ or CD8+ T cells to kill intracellular pathogens. One approach for new generation vaccines is the use of agonists for Toll-like receptors (TLRs) that activate innate immune receptors, mainly on antigen presenting cells, and facilitate the generation of T helper cell responses.

Adjuvants that are currently employed in human vaccines licensed for use in the USA and/or Europe include aluminium salts, oil-in-water emulsions (MF59, AS03 and AF03), virosomes, and AS04 (Alving, CR, et al., 2012). Among the most advanced adjuvants systems is AS04 which is used in the Cervarix® HPV vaccine and consist of the TLR4 ligand monophosphoryl lipid A (MPL) combined with aluminium salt. MPL, along with

QS21, is also part of the adjuvant system (AS01) in the RTS, S malaria vaccine from GlaxoSmithKline which has been evaluated in a Phase 3 clinical trial (Regules, JA, et al., 2011). Another clinically advanced adjuvant is CpG oligodeoxynucleotide (ODN), a TLR9 ligand contained in the Heplisav® vaccine candidate for hepatitis B from Dynavax, that has completed a Phase 3 clinical trial (Reed, SG, et al., 2013).

Small molecule immune potentiators as a new class of vaccine adjuvants

A new class of adjuvants, small molecule immune potentiators (SMIPs), has been identified that activate immune cells by targeting TLR7 and TLR8. Imiquimod and Resiquimod (R848) are clinically advanced TLR7 and/or TLR8 SMIPs that are used as immunotherapeutics. Although Imiquimod and Resiquimod have been studied extensively as vaccine adjuvants in preclinical models (Vasilakos et al. 2013), they were never optimized for this use and, in general, compare poorly to other pre-clinical and clinical adjuvant candidates. Furthermore, when Imiquimod is applied topically (it is a licensed topical treatment for viral and malignant skin lesions) it induces strong local and systemic inflammatory reactions, and is poorly tolerated (Bauza, et al. 2009; Campanelli, et al. 2005; Meyer, et al. 2008).

Unlike traditional drugs, TLR7 SMIPs activate innate immunity and initiate a cascade of immune responses that can have systemic impact and endure after the compound has been cleared from the organism. For SMIPs as vaccine adjuvants this difference is highlighted further by the fact that 2-3 local IM injections drive antigen-specific B and T cell responses at distal sites and these can provide protection in the form of immunologic memory (Tacken, et al. 2011; Ilyinskii, et al., 2014). Therefore, limiting the systemic exposure of the SMIP adjuvants has been postulated as an approach to both increase vaccine efficacy and minimize side effects associated with systemic and generalized inflammation. Novartis is currently developing a novel adjuvant, containing a SMIP from the benzonaphthryridines (BZN) series, LHD153, which targets TLR7. The objective driving the discovery of this new TLR7 ligand was to develop a vaccine adjuvant with high efficacy in increasing the vaccine specific immune response and with minimal side effects. To obtain this objective it was postulated that the ideal compound would remain localized at the site of injection to help trigger the immune reaction to vaccine antigens, yet maintain a low systemic distribution. At the same time this compound had to be soluble to make industrial scale-up and manufacturing feasible. Soluble BZN were engineered so that they could be formulated with aluminium salts with the aim of limiting their systemic exposure and keeping them localized in the muscle for short time after immunization. The strongest adsorption to aluminium hydroxide particles is obtained through ligand exchange of hydroxyl and/or phosphate groups on the surface of aluminium hydroxide or phosphate with soft anionic moieties such as phosphates, phosphonates, phosphites, sulfates and carboxylates. To drive the adsorption to

aluminium hydroxide through ligand exchange, LHD153 was functionalized with a polyethylene glycol (PEG) linker and a terminal phosphonate. Furthermore, LHD153 was stabilized with arginine salt to allow scale up for GMP manufacturing, yielding LHD153R. As predicted, unformulated LHD153R exhibited high levels of systemic exposure when injected IM in mice, rats and dogs, whereas the serum concentrations of LHD153R adsorbed to aluminium hydroxide (Aluminium Hydroxide/LHD153R) was dramatically reduced. Moreover, Aluminium Hydroxide/LHD153R remained localized to the injection site.

Preclinical studies using Aluminium Hydroxide/LHD153R to date confirm the activation of the TLR7 pathway and subsequent boost of both the humoral and cellular immune response. Moreover, Aluminium Hydroxide/LHD153R displays a unique pharmacokinetic profile as demonstrated by its minimal systemic exposure, potentially minimizing any systemic inflammatory response associated with tolerability issues. Aluminium hydroxide/LHD153R has achieved proof of concept in animal models using several vaccine antigens including MenC, MenB, rabies, HIV and respiratory syncytial virus (RSV). In vitro toxicity of LDH153R has been assessed, and in vivo nonclinical tolerability and safety of LHD153R and Aluminium Hydroxide/LHD153R have been evaluated in rats, dogs and non-human primates. LHD153R was not phototoxic, genotoxic or mutagenic (Ames and chromosomal aberration tests), and did not cause local or systemic toxicity in dogs or rats. Furthermore, Aluminium Hydroxide/LHD153R was well tolerated in rhesus monkeys.

1.2 Rationale

The aim of this study is to assess the safety of Aluminium Hydroxide/LHD153R adjuvanted MenC-CRM$_{197}$ conjugate vaccine (MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R) and to compare the antibody-mediated immune response elicited by MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R with the licensed aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®).

Furthermore, a comprehensive set of exploratory objectives has been selected to assess the systemic exposure of LHD153 after intramuscular injection and to evaluate the quality of the specific immune response against MenC-CRM$_{197}$ in detail and to evaluate biomarkers that may be predictive of safety and/or innate immune activation.

The licensed Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) has been chosen as the primary vaccine candidate to assess the safety and immunopotentiating properties of Aluminium Hydroxide/LHD153R for several reasons. Firstly, the safety and immunogenicity profiles of the Meningococcal C-CRM$_{197}$ Conjugate Vaccine have been well established through years of commercial use. Secondly, a more potent

Meningococcal C-CRM$_{197}$ Conjugate Vaccine might enable a reduction of the antigen dosage or the number of doses needed in infants between 2 and 12 months of age. Finally, the Meningococcal C-CRM$_{197}$ conjugate is a well-characterized, single antigen preparation which provides an ideal setting to explore the potential of this new Aluminium Hydroxide/LHD153R adjuvant.

2.0 OBJECTIVES

2.1 Primary Objectives

Primary Safety Objective

To assess the safety of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R as compared to that of aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine.

Primary Immunogenicity Objective

To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine at Day 29, as measured by human complement serum bactericidal assay (hSBA) directed against MenC.

2.2 Secondary Objectives

Secondary Immunogenicity Objective(s)

1. To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal CCRM$_{197}$ Conjugate Vaccine at Day 8 and Day 181 after vaccination, as measured by hSBA directed against MenC. Baseline antibody titers will also be measured by hSBA.
2. To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal CCRM$_{197}$ Conjugate Vaccine, at Day 8, Day 29 and Day 181 after vaccination, as measured by an enzyme-linked immunosorbent assay (ELISA) to MenC. Baseline antibody concentrations will also be measured by ELISA.

2.3 Exploratory Objectives

1. To evaluate the systemic exposure of LHD153 at several early time-points after IM injection of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R or Meningococcal CCRM$_{197}$ Conjugate Vaccine.
2. To explore the frequency of B cells specific for MenC polysaccharide and CRM$_{197}$ protein at baseline (Day 1) and at Day 8, Day 29 and Day 181 after vaccination with MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R or the aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine. Subsequently, the B cell repertoire of the antigen specific B cells and the specific antibody functionality will be analyzed in a selected subset of subjects.
3. To explore the baseline T cell mediated immunity to CRM$_{197}$ and to evaluate the frequency and quality of CRM$_{197}$ specific T cells induced by MenCCRM$_{197}$/Aluminium Hydroxide/ LHD153R compared to aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine at Day 8 and Day 29.
4. To evaluate biomarkers that may be predictive for safety and/or innate immune activation.

3.0 STUDY DESIGN

3.1 Overview of Study Design

This is a Phase 1, randomized, observer blind, adjuvant dosage-escalation study. It will be performed at a single center. In total, approximately 80 healthy male and healthy nonpregnant female adults (18-45 years of age) will be enrolled in the study.

Subjects will be randomized to receive a single IM vaccination of either the licensed aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (Menjugate®) or the investigational vaccine, MenC-CRM_{197}/Aluminium Hydroxide/LHD153R.

The dosage of LHD153R will be escalated from 12.5 µg to 100 µg. For the dosageescalation of LHD153R, the subjects will be enrolled into 1 of 4 cohorts, in a stepwise manner with 20 subjects per cohort. Subjects in all cohorts will be randomized in a 1:4 ratio, to receive either aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (control) or MenC-CRM_{197}/Aluminium Hydroxide/LHD153R with increasing doses of LHD153R.Subjects assigned to MenC-CRM_{197}/Aluminium Hydroxide/LHD153R in Cohort 1 will receive 12.5 µg of LHD153R; Subjects in Cohort 2 will receive 25 µg of LHD153R; Subjects in Cohort 3 will receive 50 µg of LHD153R; Subjects in Cohort 4 will receive 100 µg of LHD153R (Table 3.1-1).

Table 3.1-1: Subjects Randomized per Cohort and Treatment Dose Group

Cohort	Group	Subjects/ Group	MenC Dosage* (µg)	Adjuvant Dosages		Total Volume/Dose	Total Subjects/Group
				Aluminium Hydroxide (mg)	LHD153R (µg)		
1	A	4	10	1	0	0.5 mL	20
	B	16	10	1	12.5	0.5 mL	
2	A	4	10	1	0	0.5 mL	20
	C	16	10	1	25	0.5 mL	
3	A	4	10	1	0	0.5 mL	20
	D	16	10	1	50	0.5 mL	
4	A	4	10	1	0	0.5 mL	20
	E	16	10	1	100	0.5 mL	

*Conjugated to 12.5-25 µg CRM_{197}

All cohorts will have a staggered entry. For each cohort, the first 5 subjects (i.e. the first 1:4 randomization block) to receive either aluminium hydroxide adjuvanted

Meningococcal C-CRM$_{197}$ Conjugate Vaccine (n=1) or MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R (n=4) will be vaccinated at rate of 1 subject each day.

After entry of the first 5 subjects in each cohort, the enrollment will be paused. The remaining 15 subjects for each cohort will be enrolled only after DMC review of the safety results obtained through Day 14 has been finalized (Table 3.1-2). In addition, enrollment of the first 5 subjects of the next cohort will only proceed after the Day 14 safety results of the first 5 subjects of the previous cohort have been reviewed by the DMC. Furthermore, all available Day 14 and Day 29 safety results will be included in DMC review between the different enrollment stages.

Table 3.1-2: Overview of staggered entry of subjects based on DMC reviews

Stage	Dosage Cohort	MenC-CRM$_{197}$/ Aluminium Hydroxide (n)	MenC-CRM$_{197}$/ Aluminium Hydroxide /LHD153R (n)
1	1	1	4
Enrollment pause until DMC review of Stage 1 Day 14 Safety Results			
2	1	3	12
	2	1	4
Enrollment pause until DMC review of Stage 1 Day 29 and Stage 2 Day 14 Safety Results			
3	2	3	12
	3	1	4
Enrollment pause until DMC review of Stage 2 Day 29 and Stage 3 Day 14 Safety Results			
4	3	3	12
	4	1	4
Enrollment pause until DMC review of Stage 3 Day 29 and Stage 4 Day 14 Safety Results			
5	4	3	12

Post-vaccination procedures include collection of urine specimens at Day 8 and Day 29 for safety assessment and blood specimens at Day 8, Day 29 and Day 181 for safety assessment and evaluation of the primary and secondary immunogenicity endpoints. Furthermore, additional blood specimens will be collected for assessment of exploratory endpoints at Day 1, Day 4, Day 8, Day 29 and Day 181 from those subjects that signed an additional informed consent concerning blood collection for exploratory assessment.

3.2 Study Period

Each subject should expect to participate in the study for approximately 12 months, from the time of enrolment through the last study visit.

3.3 Blinding Procedures

This study is designed as an observer-blind study. For each dosage cohort, subjects, investigators, laboratories and the sponsor will be blinded to vaccine assignments.

To maintain the blindness within each cohort, designated nurse(s) or physician(s) will be responsible for administering the study vaccines to the subjects, and will be instructed not to reveal the identity of the study vaccines neither to the subject nor to the investigative site personnel (investigator, study nurse, monitor) involved in the conduct or monitoring of the trial. This (these) designated individual(s) will have no contact with the subjects after the administration of the study vaccine. Furthermore, unblinded monitors are assigned to reconcile actual vaccine treatment.

Study unblinding, at the group level, is planned for an Interim Analysis of the safety and immunogenicity data obtained up to Day 29 after all cohorts are enrolled and for full unblinding at the End of Study.

Except in the case of medical necessity, a subject's treatment should not be unblinded without the approval of the Sponsor. In such instance of medical emergency, every effort should be made to contact the Sponsor prior to unblinding. If unblinding should occur (by either accidental unblinding or emergency unblinding for a serious adverse event) prior to completion of the study, the investigator must promptly contact the Sponsor and document the circumstances on the appropriate forms. Instructions regarding emergency unblinding will be provided to the investigator.

3.4 Data Collection

3.4.1 Data Collected from Subjects

The following data will be collected from each subject over the duration of their study participation:

- Demographic Information
- Adverse Events
- Medical History
- Concomitant Medications
- Vital signs

All data collected must only be identified using the Subject ID, as described in section 5.2.3.

3.4.2 Tools Used for Data Collection

Data will be recorded in the Subject Diary and collected on Case Report Forms (CRFs).

Subject Diary

Subject Diaries will be the only source document allowed for solicited local and systemic adverse events (including body temperature measurements), starting after the initial 24 hours post-vaccination observation period at the clinic. The following additional rules apply to documentation of safety information collected in the Subject Diary:

1. No corrections or additions to the Subject Diary will be allowed after it is delivered to the site.
2. Any blank or illegible fields on the Subject Diary must be described as missing in the CRF.
3. Any corrections to the Subject Diary must be performed by the person completing the Subject Diary and should include a single strike through line through the incorrect value or text with a brief explanation for each change, the initials of that person, and date of correction.

Case Report Forms

This study utilizes CRFs to collect study-related data from each subject. A qualified site staff member(s) is required to enter subject data in the CRFs in English based on the medical information available in each subject's record. The following additional rules apply to documentation of Subject Diary information collected in the CRFs:

1. The site must enter all readable entries in the Subject Diary into the CRF, including those values that may be biologically implausible (e.g. body temperature: 400°C).
2. Any illegible or implausible data should be reviewed with the subject. If an underlying solicited or unsolicited adverse event is described on review with the subject, this should be described in the source document and reported as an unsolicited adverse event in the appropriate CRF (e.g., if the subject above confirms body temperature of 40°C on the day in which body temperature: 400°C was written into his/her Subject Diary, this fever of 40°C should be recorded in the appropriate CRF).

3. Any newly described safety information (including a solicited adverse event) must not be written into the Subject Diary and must be described in the study file as a verbally reported adverse event. Any adverse event reported in this fashion must be described as an unsolicited adverse event and therefore, entered in the appropriate CRF.

Data should be entered into the CRF in a timely fashion following each subject's clinic visit, study procedure, or phone call. Each subject's CRF casebook will be compared with the subject's source records by a Novartis-approved study monitor (or designee) over the duration of the study in order to ensure data collection accuracy.

3.5 Collection of Clinical Specimens

The following clinical specimens are required to be collected from each subject in this study:

- Blood
- Urine

Processing of each specimen should be completed by a qualified site member. Testing of clinical specimens will be performed by a Novartis or designated laboratory.

Blood Specimens

Before Vaccination

- At the Pre-vaccination Screening Visit (between Day -28 to -3) one sample of approximately 10 ml blood will be drawn from all subjects.
- At Visit 1 (Day 1) - prior to vaccination – two samples of approximately 10 ml blood will be drawn from all subjects.
- At Visit 1 (Day 1) - prior to vaccination - the following blood samples will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays:
  - One sample of approximately 2 ml
  - Two samples of approximately 5 ml
  - One sample of approximately 50 ml

After Vaccination

- At Visit 1 (Day 1) - 1 hour after vaccination - one sample of approximately 2 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 2 hours after vaccination - one sample of approximately 2 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 4 hours after vaccination - one sample of approximately 2 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 6 hours after vaccination – two samples of approximately 5 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 8 hours after vaccination - one sample of approximately 2 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 24 hours after vaccination - the following blood samples will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays:
  - One sample of approximately 2 ml
  - Two samples of approximately 5 ml
- At Visit 2 (Day 4) the following blood samples will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays:
  - One sample of approximately 2 ml
  - Two samples of approximately 5 ml
- At Visit 3 (Day 8) two samples of approximately 10 ml blood will be drawn from all subjects.
- At Visit 3 (Day 8) the following blood samples will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays
  - Two samples of approximately 5 ml
  - One sample of approximately 50 ml

- At Visit 6 (Day 29) two samples of approximately 10 ml blood will be drawn from all subjects.
- At Visit 6 (Day 29) one sample of approximately 50 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 9 (Day 181) one sample of approximately 10 ml blood will be drawn from all subjects.
- At Visit 9 (Day 181) one sample of approximately 50 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.

The blood will be used for screening and safety laboratory assessments, immunological serology assays, pharmacokinetic analysis, cell mediated immunity assays and gene expression and protein production assays. See section 5.1.2, section 5.2.1 and section 7.0 for additional details.

Processing of each blood specimen should be completed in accordance with the study specific Clinical Specimen Laboratory Manual.

The total amount of blood collected over the study period for all subjects will be approximately 80 ml.

For subjects that signed an additional informed consent for blood collection for exploratory assays the total amount of blood collected over the study period will be approximately 344 ml.

Urine Specimens

Urine will be collected at the Pre-vaccination Screening Visit (between Day -28- to -3), at Visit 1 (Day 1; before vaccination), at Visit 3 (Day 8) and at Visit 6 (Day 29). Results will be recorded in the source document and CRF.

Urine will be collected from all subjects for safety laboratory assessments and drugs-ofabuse testing. Furthermore, urine will be collected for pregnancy testing in all females.

3.6 Stopping/Pausing Guidelines

Stopping/pausing guidelines are predefined criteria that halt the conduct of a study (either a vaccine group or the entire study). These guidelines are used to ensure the safety of study subjects.

The following criteria, based on FDA guidance and with grading scales adapted from the CBER Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive vaccine Clinical Trials", will be used for this study:

1. The study will be halted (no new enrollments and no further investigational product administered until a full safety review by the DMC and consultation with the IRB/EC and the health authorities is completed) if one of the following occurs
   a. One subject experiences a serious adverse event (SAE) assessed as possibly or probably related to investigational product or,
   b. There is a subject death assessed as possibly or probably related to the investigational product.
2. If one or more subjects experience a Grade 4 AE (see Appendix C, D, and E), vital sign or laboratory abnormality that cannot be clearly attributed to another cause, vaccination will be suspended until a full safety review by the DMC is performed.
3. If six or more subjects experience a Grade 3 AE (see Appendix A, B, C, D, and E), vital sign or laboratory abnormality, dosage escalation will be suspended for that vaccine until a full safety review by the DMC is performed.

The sponsor or the investigator (following consultation with the sponsor) has the right to discontinue the study at any time. If the clinical study is prematurely terminated, the investigator must promptly inform the study subjects and must assure appropriate therapy and follow-up for the subjects. All procedures and requirements pertaining to the archiving of the documents must be followed. All other study materials (such as study vaccines) must be returned to the sponsor or destroyed after sponsor approval.

3.7 Data Monitoring Committee

A DMC will be formed to review safety data during scheduled periodic reviews. The DMC may also perform reviews on an ad hoc basis as needed. DMC membership will consist of at least 3 individuals who are external to the site and sponsor, and will include 1 statistician who is independent from the study team.

Subjects will be enrolled in a stepwise manner in each of the four vaccine dosage cohorts (Cohort 1: 12.5 µg LHD153R, Cohort 2: 25 µg of LHD153R, Cohort 3: 50 µg of

LHD153R and Cohort 4: 100 µg of LHD153R). The DMC will review all safety data, as described in the DMC charter and in the Statistical Analysis Plan, after the first 5 subjects in each cohort have completed Visit 4 and their data are available for analysis, and before enrollment of the remaining subjects in the respective cohort and before enrollment of the first 5 subjects in the subsequent cohort. In addition, in between the different enrollment stages, the DMC will review all available safety data of subjects that have completed Visit 4 and all available safety data of subjects that have completed Visit 6.

The specific roles and responsibilities of the DMC members and other personnel involved will be documented in the DMC charter. The DMC charter will be finalized before the start of the study and will outline in detail all pausing and stopping rules according to the Clinical Study Protocol.

3.8 Premature Withdrawal from Study

Subjects may withdraw at any time, or be dropped from the study at the discretion of the investigator should any untoward effects occur and/or for safety reasons. In addition, a subject may be withdrawn by the investigator or the Sponsor if he/she violates the study plan or for administrative reasons. The investigator or study coordinator must notify the Sponsor immediately when a subject has been withdrawn due to an adverse event.

The circumstances above are referred to as premature withdrawal from the study, and the reason for premature withdrawal should be clearly documented and detailed in the source documentation. The investigator should make every attempt to evaluate the subject's safety, including resolution of ongoing AEs, at the time of premature withdrawal. If a subject wants to withdraw from the study prior to the last planned study visit, the subject will be asked to be followed for safety for the duration of the study. When a subject withdraws, or is withdrawn, from the study, the procedures described in section 5.5.1 should be completed if possible.

The reasons for premature withdrawal from the study include: Adverse event, death, withdrawal of consent, lost to follow-up, administrative reason, and protocol deviation. These reasons are described in greater detail below.

Adverse Event

For any subject withdrawn from study participation prior to the planned Study Termination Visit, it is important to determine if an AE was associated with the reason for discontinuing the study. This AE must be identified on the appropriate CRF page by indicating "Withdrawn from study due to AE". Any ongoing AEs at the time of study withdrawal must be followed until resolution or stabilization.

Death

For any subject withdrawn from study participation due to death, this should be noted on the appropriate CRF page and the associated SAE that led to the death must be reported.

Withdrawal of consent

The subject can withdraw consent for participation in the study at any time without penalty or loss of benefit to which the subject is otherwise entitled. Reason for early termination should be deemed as "withdrawal of consent" if the subject withdraws from participation due to a non-medical reason (i.e., reason other than AE). If the subject intends to withdraw consent from the study, the investigator should clarify if the subject will withdraw completely from the study or if the subject will continue study participation for safety, or a subset of other study procedures. If the subject requests complete withdrawal from the study, no further study interventions will be performed with the subject.

Lost to Follow-Up

For subjects who fail to show up for study visits (clinic or telephone contacts), study staff is encouraged to make at least three documented attempts to contact the subject by telephone and at least one documented written attempt to contact the subject to encourage the completion of study termination procedures. These efforts to contact the subject must be recorded in the source document. The termination date for the subject to be captured on the appropriate CRF page is the date of the last contact (clinic visit or telephone) with the subject.

Administrative Reason

Examples for subjects withdrawn from the study due to administrative reason can include: Sponsor decision to terminate the study, subject meeting a pre-specified withdrawal criterion, subject discontinuation for insurance issues, moving, no time, etc. This reason should be noted in the appropriate CRF page and any ongoing AEs at the time of study withdrawal must be followed until resolution/stabilization.

If the clinical study is prematurely terminated by the Sponsor, the investigator is to promptly inform the study subjects and local EC/IRB and should assure appropriate therapy and follow up for the subjects. All procedures and requirements pertaining to the archiving of study documents should be followed. All other study materials (study medication/vaccines, etc.) must be returned to the Sponsor.

For subjects who are withdrawn from the study due to receipt of an excluded medication/vaccination or due to significant protocol non-compliance, this reason should be noted in the appropriate CRF page.

Protocol Deviation

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. In general, subjects associated with protocol deviations may remain in the study unless continuation in the study jeopardizes the subject's health, safety, or rights.

Investigators will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a change to the protocol would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/EC and health authorities it cannot be implemented.

Any subject who becomes pregnant during the study should be encouraged to continue participating in the study for safety follow-up. The site must complete a Pregnancy Report CRF (initial report) as soon as possible after learning of pregnancy occurrence (see section 7.1.6 for further details). If the subject withdraws from the study for any of the above categories except death, the site will obtain permission from the subject to continue to remain in contact with her until the outcome of the pregnancy is known, even if the outcome is not known until after the subject reaches the end of the routine study period.

3.9 End of Study

Most clinical trials intended to support the efficacy/immunogenicity and safety of an Investigational Product proceed to full completion of planned sample size accrual.

A subject is considered to have completed this study when he/she has: (1) received the intended dose of study vaccine and (2) completed 365 days (Visit 12) of safety follow-up after receiving the study vaccine.

Evaluation of the primary and secondary immunogenicity objectives requires the testing of biological samples from all study subjects, which can only be completed after all samples are collected. The last samples for the analysis of the primary and/or secondary objectives will be taken at Visit 9 (Day 181). For the purpose of this protocol, End of

Study is defined as the completion of the testing of such biological samples, to be achieved no later than 8 months after collection of the last biological sample at Visit 9.

4.0 SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

In order to participate in this study, all subjects must meet all of the inclusion criteria described.

1. Male or female individuals of 18 through 45 years of age on the day of informed consent.
2. Healthy volunteers with good physical and mental health status, determined on the basis of the medical history, a physical examination and the results of the screening tests as judged by the investigator.
3. Individuals who have voluntarily given written informed consent after the nature of the study has been explained according to local regulatory requirements, prior to study entry.
4. Individuals who can comply with study procedures including follow-up[1].
5. Individuals that are able to understand, read and write German language.
6. Females of childbearing potential who are using an effective birth control method[2] which they intend to use for at least 30 days after the study vaccination.

4.2 Exclusion Criteria

Each subject must not have or must not be:

1. Progressive, unstable or uncontrolled clinical conditions.
2. Hypersensitivity, including allergy, to any component of vaccines, medicinal products or medical equipment whose use is foreseen in this study.

[1] A subject is considered to be compliant if the Investigator judges that the subject will complete the Subject Diary, return for all the follow-up visits and be available for telephone calls as scheduled in the study.

[2] The following birth control methods are considered effective:

- Hormonal contraceptive (such as oral, injection, transdermal patch, implant) if used for at least 30 days prior to informed consent
- Diaphragm with spermicide, tubal occlusion device
- Intrauterine device (IUD)

- Tubal ligation
- Male partner using condom with spermicide
- Male partner having been vasectomized at least six months prior to informed consent

3. Clinical conditions representing a contraindication to intramuscular vaccination and blood draws.
4. Abnormal function of the immune system resulting from:
   a. Clinical conditions.
   b. Systemic administration of corticosteroids (PO/IV/IM) for more than 14 consecutive days within 90 days prior to informed consent.
   c. Administration of antineoplastic and prescription immunomodulating agents or radiotherapy within 90 days prior to informed consent.
5. Received immunoglobulins or any blood products within 180 days prior to informed consent.
6. Received an investigational or non-registered medicinal product within 30 days prior to informed consent or intend to participate in another clinical study at any time during the conduct of this study.
7. Vulnerable subjects (e.g. persons kept in detention), study personnel or an immediate family or household member of study personnel, subjects with legal incapacity or limited legal capacity
8. Any relevant deviation from the laboratory parameters at screening as judged by the investigator.
9. Previously received any vaccine that included a MenC antigen.
10. Previously suspected or confirmed disease caused by *N. meningitides.*
11. Had household contact with and/or intimate exposure to an individual with culture proven MenC.
12. A positive serum or urine pregnancy test prior to the study vaccine administration or are currently lactating.
13. A positive drugs-of-abuse test prior to the study vaccine administration

14. Received any other vaccines within 30 days prior to enrolment in this study or who are planning to receive any vaccine within 30 days from the administration of study vaccines.
15. Any other condition that, in the opinion of the investigator, might interfere with the results of the study or pose additional risk to the subject due to participation in the study.

4.3 Criteria for Delay of Vaccination or Blood Draw

There may be instances when individuals meet all eligibility criteria for vaccination or blood draw yet have a transient clinical circumstance which may warrant delay of vaccination or blood draw. Under such circumstances, a subject may be considered eligible for study enrolment after the appropriate window for delay has passed and inclusion/exclusion criteria have been rechecked, and if the subject is confirmed to be eligible.

Reasons for delay of vaccination include:

- Body temperature elevation ≥38.0°C (measured orally) within 3 days prior to intended study vaccination.
- Use of antipyretics and/or analgesic medications within 24 hours prior to vaccination.

Reasons for delay of blood draw include:

- Subject has received a dose of systemic antibiotics less than 6 days before blood collection for the hSBA directed against MenC.

5.0 STUDY PROCEDURES

The sections that follow provide an overview of the procedures that are to be followed in enrolling, evaluating, and following subjects who participate in this clinical study. Visits can be either clinic visits or safety follow-up telephone calls, as specified in the Table below and in the Time and Events Tables 3 and 4 of the Study Synopsis.

Table 5.0-1: Study procedures

Visit Category	Procedures
Pre-vaccination Clinic Visit	Section 5.1 describes procedures to be followed prior to subject enrollment, including: informed consent and screening procedures.
Vaccination Clinic Visit	Section 5.2 describes procedures to be followed during the vaccination clinic visit, including: prevaccination procedures, enrolment, randomization, vaccination and post-vaccination procedures.
Post-vaccination Visits	Section 5.3 describes follow-up clinic visits and safety follow-up calls.
Unscheduled Visits	Section 5.4 describes possible procedures to be followed at unscheduled clinic visit.
Study Termination Visit	Section 5.5 describes procedures to be followed at the last study visit for a subject (may include early termination visit).

5.1 Pre-vaccination Clinic Visit(s)

The Pre-vaccination Clinic Visit must be performed in the period between Day -28 and Day -3.

This section describes the procedures that must be performed for each potential subject prior to enrollment, including obtaining informed consent and screening.

5.1.1 Informed Consent

"Informed consent" is the voluntary agreement of an individual or his/her legal guardian(s) to participate in research. Consent must be given with free will of choice, and without undue inducement. The individual must have sufficient knowledge and understanding of the nature of the proposed research, the anticipated risks and potential benefits, and the requirements of the research to be able to make an informed decision.

Informed consent following local IRB/EC guidance **must** be obtained before conducting any study-specific procedure (i.e., all of the procedures described in the protocol). Prior to any additional blood sample collection for exploratory objectives, a secondary informed consent **must** be signed by subjects. The process of obtaining informed consent should be documented in the subject source document in addition to maintaining a copy of the signed and dated informed consent.

5.1.2 Screening

After an individual has consented to participate in the study and informed consent is signed, that individual will be given a unique Screening Number. The subject's unique Screening Number will be documented in the Screening and Enrolment log. The eligibility of the subject will be determined based on the inclusion and exclusion criteria listed in section 4.0 and evaluated during this screening procedure.

Screening procedures at the Pre-vaccination Clinical Visit (between Day -28 and Day -3) will include the following:

- Review of demographic data, including age, gender, race, body weight and height.
- Review of medical history, including but not limited to any medical history, ongoing illnesses or injuries that may be relevant to subject eligibility for study participation. Relevant medical history can also include any medical history that contributes to the understanding of an adverse event that occurs during study participation, if it represents an exacerbation of an underlying disease/pre-existing problem.
- Perform physical examination, including but not limited to:
  - Assessment of general appearance
  - Collection of vital signs, including body temperature, blood pressure, heart rate and respiratory rate
  - Examination of head, ears, eyes, nose and throat (HEENT)
  - Examination of skin
  - Auscultation of heart and lungs
- Collection and review of prior and concomitant medications or vaccinations taken prior to start of study (refer to section 6.5 for further details).
- Collection of any unsolicited AEs occurring prior to administration of the study vaccine.

- Blood draw (approximately 10 ml) for Safety Laboratory assessments, measurement of Hepatitis B surface antigen, anti-Hepatitis C virus antibodies, anti-HIV 1 and 2 antibodies and serum pregnancy test (all women).
- Urine sample for Safety Laboratory assessments and drugs-of-abuse testing.

NOTE: A general physical examination is to be performed by a qualified health care practitioner. "Qualified health care practitioner" refers to any licensed health care professional who is permitted by institutional policy to perform physical examinations and who is identified within the Study Staff Signature Log.

Data collected during the Pre-vaccination Screening Clinic Visit must be written in the source document (see section 9.1) and will be captured in the screening CRF Forms. In the event that the individual is determined ineligible for study participation, he/she is considered a screen failure. The reason for screen failure must be documented in the Screening and Enrolment log.

5.2 Vaccination Clinic Visit(s)

This section describes the procedures to be performed at the Vaccination Clinic Visit (Visit 1, Day 1), including: pre-vaccination procedures, enrolment, randomization, prevaccination blood draw, vaccination and post-vaccination procedures.

5.2.1 Pre-vaccination Procedures

During pre-vaccination procedures at Visit 1 (Day 1), the eligibility of the subject will be confirmed based on the inclusion and exclusion criteria listed in section 4.0.

Pre-vaccination procedures at Visit 1 (Day 1) will include the following:

- Review of systems by means of a structured interview that queries the subject as to any complaints the subject has experienced across each organ system.
- Perform physical examination, including but not limited to:
  - Assessment of general appearance
  - Assessment of body weight and collection of vital signs, including body temperature, blood pressure, heart rate, and respiratory rate
  - Examination of head, ears, eyes, nose and throat (HEENT)
  - Examination of skin

- Auscultation of heart and lungs

- Collection and review of prior and concomitant medications or vaccinations taken, or recalled, since the last visit (refer to section 6.5 for further details).
- Collection of any unsolicited AEs occurring prior to administration of the study vaccine.
- One blood sample (approximately 10 ml) will be drawn from all subjects for serology testing.
- One blood sample (approximately 10 ml) will be drawn from all subjects for baseline Safety Laboratory assessments.
- Urine sample for baseline Safety Laboratory assessments, pregnancy testing (all women) and drugs-of-abuse testing.
- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and volume of blood draws are provided in section 3.5.

NOTE: A general physical examination is to be performed by a qualified health care practitioner. "Qualified health care practitioner" refers to any licensed health care professional who is permitted by institutional policy to perform physical examinations and who is identified within the Study Staff Signature Log.

Data collected during pre-vaccination procedures at Visit 1 must be written in the source document (see section 9.1). In the event that the individual is determined ineligible for study participation, he/she is considered a screen failure. The reason for screen failure must be documented in the Screening and Enrolment log. If the individual is determined to be eligible for the study, he/she can be enrolled into the study.

5.2.2 Enrolment

After an individual is determined to be eligible for study participation, the investigator will enroll the subject into the Electronic Data Capture (EDC) system where the randomization to the treatment group will occur. The Screening Number ceases to be used and remains in the Screening and Enrolment Log only.

If for any reason, after signing the informed consent form (ICF), the subject who is eligible and enrolled fails to be randomized, this is called a randomization failure. In this case the early termination study procedures must be applied. The reason for all randomization failures should be recorded in the Screening and Enrolment Log and in the

source document as specified in the Source Data Agreement. The information on subjects who are randomization failures should be kept distinct from subjects who are screen failures, as described in section 5.1.2 and section 5.2.1.

5.2.3 Randomization

Enrolled subjects will be randomized and automatically assigned a unique Subject ID. The Subject ID will be the subject's unique identification number for all CRFs and associated study documentation that will be used for the duration of the study.

If for any reason, after signing the informed consent form (ICF), the eligible subject is enrolled and randomized but fails to undergo treatment, this is an Early Termination and the reason should be recorded in source document as specified in the Source Data Agreement/Source Data Verification Form. The information on these Early Termination subjects should be kept distinct in the source documentation from randomization failures, which are described in section 5.2.2.

5.2.4 Vaccination

After completing the pre-vaccination procedures at Visit 1 (Day 1), administer the vaccine to the subject according to the procedures described in section 6.3. Observe the blinding procedures described in section 3.3.

5.2.5 Post-vaccination Procedures

The following post-vaccination procedures will be performed at Visit 1 (Day 1):

- After vaccination, the subject will be observed for at least 30 minutes for any immediate solicited and unsolicited AEs and a body temperature measurement at 30 min after vaccination. All safety and body temperature data collected during this time are to be recorded in the subject's source document.
- After vaccination, the subject will be observed for at least 24 hours at the clinic including observation for solicited and unsolicited AEs and body temperature measurements . Body temperature measurements must be performed at 2, 4, 6, 8, 10, 12, 20 and 24 hours after vaccination. All safety and body temperature data collected during this time are to be recorded in the subject's source..
- From those subjects that signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn in the first 24 hours after vaccination. Details regarding the number and volume of post-vaccination blood draws are provided in section 3.5.

After the initial 24 hours inpatient observation period, a Subject Diary will be used in this study to document solicited and unsolicited AEs until Day 14. The Subject Diary is the only source for collection of solicited AEs after the initial 24 hours inpatient observation period. Therefore, it is critical that the subject completes the Subject Diary correctly.

The following training regarding completion of the Subject Diary must be provided:

- The subject should be trained on how and when to complete each field of the Subject Diary.
- The subject should be trained on how to self-measure local solicited adverse events and body temperature. The measurement of solicited local adverse events is to be performed using the ruler provided by the site.
- The subject should be instructed how to perform body temperature measurement using the thermometer provided by the site. If the subject feels unusually hot or cold during the day, the subject should check their body temperature. If the subject has fever, the highest body temperature observed that day should be recorded in the Subject Diary.

Subject Diary training should be directed at the individual(s) who will perform the measurements of adverse events and who will enter the information into the Subject Diary. This individual may not be the subject, but if a person other than the subject enters information into the Subject Diary, this person's identity must be documented in the Subject Diary. Any individual that writes in the Subject Diary must receive training on completion of the Diary Card at the time of the visit. This training must be documented in the subject's source record.

The site should schedule the next study activity (clinic visit) with the subject.

The subject will receive a written reminder of the next planned study activity. The subject will be reminded to complete the Subject Diary and to contact the site if there are any questions, and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

5.3 Post-vaccination Visit(s)

5.3.1 Subject Diary Reminder, Safety Follow-up and/or Post-vaccination Blood Draw Clinic Visits

Subject Diary reminder, Safety follow-up and/or post-vaccination blood draw clinic visits will be performed on Day 4 (Visit 2), Day 8 (Visit 3), Day 15 (Visit 4), Day 29 (Visit 6), Day 85 (Visit 7), Day 113 (Visit 8) and Day 181 (Visit 9)

At Day 4 (Visit 2) the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. All unsolicited AEs, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. Any concomitant medications or vaccinations associated with those events must also be recorded on the source documents.
- All subjects will be reminded to complete the Subject Diary and to contact the site if there are any questions, and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit. No changes to the Subject Diary should be done at the clinic visit.
- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and volume of blood draws are provided in section 3.5.
- The site should schedule the next study activity (clinic visit) with the subject and the subject will receive a written reminder of the next planned study activity.

At Day 8 (Visit 3) the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. All unsolicited AEs, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. Any concomitant medications or vaccinations associated with those events must also be recorded on the source documents.
- The subject will be reminded to complete the Subject Diary and to contact the site if there are any questions, and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to hospitalization

or an emergency room visit. No changes to the Subject Diary should be done at the clinic visit. Blood draw (approximately 10 ml) from all subjects for Safety Laboratory assessments.

- Urine sample from all subjects for Safety Laboratory assessments.
- Blood draw (approximately 10 ml) from all subjects for serology testing.
- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and volume of blood draws are provided in section 3.5.
- The site should schedule the next study activity (clinic visit) with the subject and the subject will receive a written reminder of the next planned study activity.

At Day 15 (Visit 4) the following procedures will be performed:

- The Subject Diary will be collected and reviewed. No changes to the Subject Diary should be done at the clinic visit. For details on the Subject Diary see sections 3.4.2, and 5.2.5. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. All unsolicited AEs until Day 14, solicited local and systemic AEs persisting at Day 14, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. All concomitant medications or vaccinations associated with those events must also be recorded on the source documents.
- The site should schedule the next study activity (safety phone call) with the subject.
- The subject will receive a written reminder of the next planned study activity. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

At Day 29 (Visit 6) the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. Any solicited local and systemic AEs continuing beyond Day 14, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. All concomitant

medications or vaccinations associated with those events must also be recorded on the source documents.

- Blood draw (approximately 10 ml) from all subjects for Safety Laboratory assessments.
- Urine sample from all subjects for Safety Laboratory assessments.
- Blood draw (approximately 10 ml) from all subjects for serology testing.
- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and volume of post-vaccination blood draws are provided in section 3.5.
- The site should schedule the next study activity (clinic visit) with the subject.
- The subject will receive a written reminder of the next planned study activity. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

At Day 85 and Day 113 (Visit 7 and Visit 8), the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. Any solicited local and systemic AEs continuing beyond Day 14, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. All concomitant medications or vaccinations associated with those events must also be recorded on the source documents.
- The site should schedule the next study activity (clinic visit) with the subject.
- The subject will receive a written reminder of the next planned study activity. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

At Day 181 (Visit 9), the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since

the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. Any solicited local and systemic AEs continuing beyond Day 14, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. All concomitant medications or vaccinations associated with those events must also be recorded on the source documents.

- Blood draw (approximately 10 ml) from all subjects for serology testing.
- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and volume of post-vaccination blood draws are provided in section 3.5.
- The site should schedule the next study activity (safety phone call) with the subject.
- The subject will receive a written reminder of the next planned study activity. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

5.3.2 Safety Follow-up Calls

Safety follow-up calls will be performed on Day 22 (Visit 5), Day 209 (Visit 10) and Day 271 (Visit 11) and include the following procedures:

- Safety follow-up calls are calls made to the subject by a healthcare professional designated on the site log. These calls will follow a script which will facilitate the collection of relevant safety information. The subject will be interviewed according to the script, and information relating to solicited local and systemic AEs persisting beyond Day 14 and unsolicited adverse events including SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal, and/or NOCD and concomitant medications or vaccinations associated with those events. All safety information described by the subject must be written down in a designated location within the source document and not written on the script used for the telephone call.
- The site should schedule the next study activity (clinic visit or study termination visit) with the subject.
- The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

5.4 Unscheduled Visits

An unscheduled visit describes a non-routine study visit triggered by a specific event. These could include anticipated or unanticipated adverse events or interventions.

The following procedures should be carried out for all unscheduled visits:

1. Evaluate the subject's vital signs body temperature, heart rate, and blood pressure and perform a symptom-directed physical examination.
2. Record any observed AEs in the source documents.
3. Record any concomitant medications or vaccinations associated with AEs in the source documents.

5.5 Study Termination Visit

The study termination visit is scheduled on Day 366 (Visit 12). The termination visit is a clinic visit. For visit procedures to be performed for a subject whose planned study participation ends prematurely, please see section 5.5.1.

At the Study Termination clinic visit the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit.
- The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present.
- Medically attended AEs, SAEs, NOCDs, or AESIs will be recorded on source documents.
- All medications taken or vaccines received will also be recorded on the source documents.
- The site will review with the subject the plan of when information relating to the subject's participation in the study may be available (e.g., study results, treatment assignments). It will also be discussed how information relating to the subject's participation in the study will be shared with the subject's healthcare provider, if the subject chooses to share this information.
- The site will complete the termination CRF page and this will mark the completion of the subject's participation in the study.

5.5.1 Early Termination Visit

The date of termination is the date of the last contact in which the subject's health status was assessed or, in cases where the subject does not agree to any further safety follow-up, it is the date consent is withdrawn. This date should be recorded on the appropriate CRF page.

When a subject is withdrawn from treatment or withdraws from the study, the investigator will notify the Sponsor and, when possible, will perform the procedures listed below.

The reason(s) for the early termination must be included in the subject's source documentation. If the Early Termination Visit is a telephone call, collect as much information as possible. Early Termination Visits include subjects who were randomized but not treated.

At the clinic visit or during the telephone call, the following procedures should be performed, when possible:

- Collection and review of Subject Diary (if not already collected).
- Interview of subject to collect unsolicited adverse events, medically attended AEs, AEs leading to withdrawal, SAEs, AESIs, and NOCD.
- Interview of subject to collect concomitant medications and/or vaccinations.
- Symptom-directed physical assessment, at least including measurement of vital signs (body temperature, respiratory rate, blood pressure, heart rate) and a check of general appearance (in case of clinic early termination visit).
- Draw a blood sample (approximately 10 ml) and a urine sample for Safety Laboratory assessment (in case of clinic early termination visit).
- The site will review with the subject the plan of when information relating to the subject's participation in the study may be available (e.g., study results, treatment assignments). It will also be discussed how information relating to the subject's participation in the study will be shared with the subject's healthcare provider, if the subject chooses to share this information.
- The site will complete the appropriate CRF page and this will mark the completion of the subject's participation in the study.

6.0 TREATMENT OF SUBJECTS

All vaccines associated with this study are to be stored separately from other vaccines and medications in a secure location under appropriate storage conditions with temperature monitoring. **All vaccines associated with this study must be checked for expiration date prior to use. Expired vaccines must not be administered to subjects.**

6.1 Study Vaccine(s)

The term 'study vaccine' refers to those vaccines provided by the Sponsor, which will be evaluated as part of the study objectives. The study vaccines specific to this study are described in Table 6.1-1.

Table 6.1-1: Study Vaccine Composition

Group A (Control) Meningococcal C-CRM$_{197}$ Conjugate Vaccine	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM$_{197}$ protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
Sodium Chloride	3.5 mg
Sterile water for injection, up to	0.5 ml

Group B (12.5µg LHD153R) - MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	

Meningococcal C oligosaccharide conjugated to	10 µg
CRM_{197} protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide/LHD153R Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
LHD153R	12.5 µg
Sodium Chloride	3.4 mg
Histidine	0.1 mg
Tris	30 µg
Sterile water for injection, up to	0.5 ml
Group C (25 µg LHD153R) - MenC-CRM_{197}/Aluminium Hydroxide/LHD153R	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM_{197} protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide/LHD153R Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
LHD153R	25 µg
Sodium Chloride	3.4 mg
Histidine	0.2 mg
Tris	61 µg
Sterile water for injection, up to	0.5 ml

Group D (50µg LHD153R) - MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM$_{197}$ protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide/LHD153R Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
LHD153R	50 µg
Sodium Chloride	3.2 mg
Histidine	0.4 mg
Tris	121 µg
Sterile water for injection, up to	0.5 ml
Group E (100µg LHD153R) - MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM$_{197}$ protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg

Aluminum Hydroxide/LHD153R Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
LHD153R	100 µg
Sodium Chloride	2.9 mg
Histidine	0.8 mg
Tris	243 µg
Sterile water for injection, up to	0.5 ml

6.2 Non-Study Vaccines

The term 'non-study vaccine' refers to those vaccines which will be intentionally given to study subjects but not formally included in the analysis of study objectives.

No non-study vaccines are planned for this study. Any non-study vaccines administered during the study conduct will be captured in the CRF as concomitant medications and/or vaccinations.

6.3 Vaccine Preparation and Administration

The investigator or designee will be responsible for oversight of the administration of vaccine to subjects enrolled in the study according to the procedures stipulated in this study protocol. All vaccines will be administered only by unblinded personnel who are qualified to perform that function under applicable local laws and regulations for the specific study site.

The vaccine components will be provided in 5 separate kits (i.e. one for the control and one for each of the 4 dosage groups). The vaccine components must be mixed prior to vaccination taking into account the appropriate aseptic procedures. Detailed vaccine preparation and administration instructions, including the maximal administration period, will be provided to investigators prior to study start and must be filed in the Investigator Site File.

PRECAUTIONS TO BE OBSERVED IN ADMINISTERING STUDY VACCINE:

- Prior to vaccination, subjects must be determined to be eligible for study vaccination and it must be clinically appropriate in the judgment of the investigator to vaccinate. Eligibility for vaccination prior to first study vaccine administration is determined by evaluating the entry criteria outlined in protocol sections 4.0.

- Study vaccines must not be administered to individuals with known hypersensitivity to any component of the vaccines.

- Standard immunization practices are to be observed and care should be taken to administer the injection intramuscularly. Before administering vaccine, the vaccination site is to be disinfected with a skin disinfectant (e.g., 70% alcohol). Allow the skin to dry. **DO NOT inject intravascularly**.

- As with all injectable vaccines, trained medical personnel and appropriate medical treatment must be readily available in case of anaphylactic reactions following vaccine administration. For example, epinephrine 1:1000, diphenhydramine, and/or other medications for treating anaphylaxis should be available.

6.4 Vaccine Administration Error or Overdose of Vaccine

Vaccine administration error is defined as receiving a dose of study vaccine that was not reconstituted as instructed or administered by a different route from the intended route of administration. An overdose of study vaccine (whether accidental or intentional) is defined when a dosage higher than the recommended dosage is administered in one dose of study vaccine.

Any vaccine administration error or overdose of study vaccine detailed in this protocol must be reported as an adverse event, and if the vaccine administration error or overdose is associated with a serious adverse event, it must be reported as such within 24 hours to the Sponsor.

6.5 Prior and Concomitant Medications and Vaccines

All medications, vaccines and blood products taken or received by the subject within 180 days prior to the start of the study are to be recorded in the appropriate CRF.

Medications taken for prophylaxis are those intended to prevent the onset of symptoms. Medications taken for treatment are intended to reduce or eliminate the presence of symptoms that are present.

NOTE: Use of antipyretics/analgesics within 24 hours prior to vaccine administration is a reason to delay study vaccination (see section 4.3).

Concomitant medications include all medications (including vaccines) taken by/administered to the subject at and after enrolment and must be documented in the appropriate CRF.

When recording concomitant medications/vaccines, they should be checked against the study entry criteria in section 4.0, to ensure that the subject should be enrolled in the study.

6.6 Vaccine Supply, Labeling, Storage and Tracking

The Sponsor will ensure the following:

- Supply the study vaccines.
- Appropriate labeling of all study vaccines provided that complies with the legal requirements of each country where the study is to be performed.

The investigator must ensure the following:

- Acknowledge receipt of the study vaccines by a designated staff member at the site, including:
  - Confirmation that the vaccines were received in good condition
  - Confirmation to the Sponsor of the temperature range during shipment from the Sponsor to the investigator's designated storage location
  - Confirmation by the Sponsor that the vaccines are authorized for use.
- Proper storage of the study vaccines, including:
  - Storage in a secure, locked, temperature-controlled location.
  - Proper storage according to the instructions specified on the labels.
  - Appropriate record keeping and inventory of the study vaccines, including regular documentation of adequate storage temperature.
- Appropriate use of the study vaccines, including:
  - No use of vaccines prior to receipt of authorization for use from the Sponsor.
  - Use only in accordance with the approved protocol.
  - Proper handling, including confirmation that the vaccine has not expired prior to administration.
  - Appropriate documentation of administration of vaccines to study subjects including:
    - Date, dosage, batch/lot numbers, expiration dates, unique identifying numbers assigned to subjects and study vaccines, and time of vaccine

administration. This information will be maintained in an accountability log that will be reviewed by the site monitor.

- Reconciliation of all vaccines received from the Sponsor. Reconciliation is defined as maintaining records of which and how many vaccines were received, which vaccines were administered to subjects, which vaccines were destroyed at the site, and which vaccines were returned to the Sponsor, as applicable.

- Proper adherence to the local institutional policy with respect to destruction of study vaccines.
- Complete record keeping of vaccine use, wastage, return or destruction, including documentation of:
  - Copy of the site's procedure for destruction of hazardous material.
  - Number of doses destroyed, date of destruction, destruction code (if available), method of destruction, and name of individual performing destruction.

Vaccines that have been stored differently from the manufacturer's indications **must not** be used unless the Sponsor provides written authorization for use. In the event that the use cannot be authorized, the Sponsor will make every effort to replace the vaccine supply. All vaccines used in conjunction with this protocol must be stored separately from normal hospital/practice stocks to prevent unintentional use of study vaccines outside of the clinical study setting.

Monitoring of vaccine accountability will be performed by the study monitor during site visits and at the completion of the study.

At the conclusion of the study, and as appropriate during the course of the study, the investigator must ensure that all unused study vaccines, packaging and supplementary labels are destroyed locally (upon approval from Sponsor) or returned to the Sponsor.

7.0 ASSESSMENTS

7.1 Safety Assessment

The measures of safety used in this study are based on previous study data and based on comparable routine clinical/laboratory procedures. They include a close vigilance for, and stringent reporting of selected local and systemic adverse events routinely monitored in vaccine studies as indicators of reactogenicity.

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

The period of observation for AEs extends from the time the subject signs informed consent until he or she completes the specified safety follow-up period (Day 366) or terminates the study early (whichever comes first). AEs occurring after the informed consent form is signed but prior to receiving study vaccine/product will be documented as an adverse event and recorded within the source documents. However, any AEs occurring prior to receipt of any study vaccine will be analyzed separately from “treatment emergent” AEs (AEs occurring after administration of the first study vaccine).

Adverse events are collected as either solicited or unsolicited adverse events. Solicited events are derived from organized data collection systems, such as Subject Diaries or interview.

7.1.1 Solicited Adverse Events

The term “reactogenicity” refers to solicited signs and symptoms (“solicited adverse events”) occurring in the hours and days following a vaccination, to be collected by the subject after the first 24 hours inpatient observation period at Day 1until Day 14, using a pre-defined Subject Diary.

The following solicited adverse events are included in the Subject Diary. Each adverse event is to be assessed using the scoring system shown in Appendix A (Solicited Local AEs) and Appendix B (Solicited Systemic AE):

Solicited Local Adverse Events

Solicited local AEs include:

- injection site erythema
- injection site induration
- injection site pain
- injection site swelling **Solicited Systemic Adverse Events**

Solicited systemic AEs include:

- body temperature ≥38.0°C (as measured orally)
- loss of appetite
- nausea
- fatigue
- generalized myalgia
- generalized arthralgia
- headache
- chills
- vomiting
- diarrhea
- generalized rash
- urticaria

Other Solicited Data

Other solicited data collected per Subject Diary include:

- Use of analgesics/antipyretics recorded as “absent” or “present” and summarized by “for treatment” or “for prophylaxis”
- Body temperature as recorded daily, ideally at same time, by the oral route

The study staff must review the data entered into the Subject Diary as described in sections 3.4.2 and 5.3.1.

NOTE: Any solicited adverse event that meets any of the following criteria must be entered into the subjects' source documents (see section 9.1) and also as an adverse event in the appropriate CRF:

- Solicited local or systemic adverse event that continues beyond Day 14 after vaccination.
- Solicited local or systemic adverse event that leads to a visit to a healthcare provider (medically attended adverse event, see section 7.1.3).
- Solicited local or systemic adverse event leading to the subject withdrawing from the study or the subject being withdrawn from the study by the investigator (adverse event leading to withdrawal, see section 7.1.3).
- Solicited local or systemic adverse event that otherwise meets the definition of a serious adverse event (see section 7.1.4).

7.1.2 Unsolicited Adverse Events

An unsolicited adverse event is an adverse event that was not solicited using a Subject Diary and that was spontaneously communicated by a subject who has signed the informed consent.

7.1.3 Evaluation of Adverse Events

Every effort should be made by the investigator to evaluate safety information reported by a subject for an underlying diagnosis and to capture this diagnosis as the event in the AE page. In other words, the practice of reporting only symptoms (e.g., "cough" or "ear pain") are better reported according to the underlying cause (e.g., "asthma exacerbation" or "otitis media").

The severity of events reported on the appropriate CRF page will be determined by the investigator as:

Mild: transient with no limitation in normal daily activity.
Moderate: some limitation in normal daily activity.
Severe: unable to perform normal daily activity.

The relationship of the study treatment to an AE will be determined by the investigator based on the following definitions:

1. Not Related

The AE is not related to an investigational vaccine if there is evidence that clearly indicates an alternative explanation. If the subject has not received the vaccine, the timing of the exposure to the vaccine and the onset of the AE are not reasonably related in time, or other facts, evidence or arguments exist that reasonably suggest an alternative explanation, then the AE is not related.

2. Possibly Related

The administration of the investigational vaccine and AE are considered reasonably related in time and the AE could be explained by exposure to the investigational vaccine or by other causes.

3. Probably Related

Exposure to the investigational vaccine and AE are reasonably related in time and no alternative explanation has been identified.

The relationship of the study treatment to an unsolicited AE will be determined by the investigator.

Note: solicited AEs will not be evaluated for relationship to study treatment. Grading for severity of solicited local and systemic AEs is described in Appendix A and Appendix B.

Adverse events will also be evaluated by the investigator for the co-existence of any of the other following conditions:

- "Medically attended adverse event": an adverse event that leads to a visit to a healthcare provider.
- "New onset of chronic disease" (NOCD): an adverse event that represents a new diagnosis of a chronic medical condition that was not present or suspected in a subject prior to study enrolment.
- AEs leading to withdrawal: adverse events leading to study or vaccine withdrawal.

All AEs, regardless of severity, will be monitored until resolution or until the investigator assesses them as chronic or stable. All subjects experiencing AEs - whether considered associated with the use of the study vaccine or not - must be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible.

7.1.4 Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose results in one or more of the following:

- Death.
- Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe.
- Required or prolonged hospitalization.
- Persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions).
- Congenital anomaly/or birth defect.
- An important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

Adverse events which do not fall into these categories are defined as non-serious.

It should be noted that a severe adverse event need not be serious in nature and that a serious adverse event need not, by definition, be severe.

Serious adverse events will be captured both on the Vaccines Serious Adverse Event (VSAE) form as well as on the appropriate CRF page. All SAEs will be evaluated by the investigator for relationship of the event to study vaccine. SAEs that are judged to be possibly or probably related to the study vaccine should be reported to the Sponsor as related/suspected events.

The relationship of the study treatment to an SAE will be determined by the investigator based on the following definitions:

1. Related/suspected

The SAE is judged by the investigator to be possibly or probably related to the study vaccine on the appropriate CRF page (see section 7.1.3).

2. Not Related

The SAE is not related if exposure to the study vaccine has not occurred, **or** the occurrence of the SAE is not reasonably related in time, **or** the SAE is considered unlikely to be related to use of the study vaccine, i.e., there are no facts (evidence) or arguments to suggest a causal relationship.

The relationship of the study vaccine to an SAE will be determined by the investigator.

In addition, SAEs will be evaluated by the Sponsor or designee for "expectedness." An unexpected AE is one that is not listed in the current Summary of Product Characteristics or the Investigator's Brochure or an event that is by nature more specific or more severe than a listed event.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the appropriate CRF. If the onset of an event occurred before the subject entered the study (e.g., any pre-planned hospitalization for conditions like cosmetic treatments or for non-emergency routine visits for a pre-existing condition), the hospitalization would not lead to an AE being classified as serious unless, in the view of the investigator, hospitalization was prolonged as a result of participation in the clinical study or was necessary due to a worsening of the pre-existing condition.

7.1.4.1 Adverse Events of Special Interest

Certain adverse events of special interest (AESIs) are monitored after the administration of immunostimulatory agents. All subjects enrolled in this study will be monitored for AESIs for the entire follow-up period. The AESIs will be defined according to MedDRA preferred terms. The investigator will be provided with a list of AESIs prior to study start. Receipt of this list will be notified and stored, along with the list of AESIs, in the Investigator Site File. During the course of the trial the list of AESIs may change. If this occurs, the investigators will be advised of the change and confirmation of receipt will be documented. The updated list of AESIs and documentation of receipt are also stored in the Investigator Site File. The occurrence of any of these adverse events will be treated as a serious adverse event (SAE), meeting the criterion of a "medically important event."

Subjects will be assessed for diagnosis of an AESI at the following visits:

- Pre-vaccination clinic visit (Day -28 to Day -3)
- Visit 1 (Day 1, pre-vaccination)
- Visit 2 (Day 4)

- Visit 3 (Day 8)
- Visit 4 (Day 15)
- Visit 5 (Day 22; Safety Follow-Up Call)
- Visit 6 (Day 29)
- Visit 7 (Day 85)
- Visit 8 (Day 113)
- Visit 9 (Day 181)
- Visit 10 (Day 209; Safety Follow-Up Call)
- Visit 11 (Day 271; Safety Follow-Up Call)
- Visit 12 (Day 366; Study Termination Visit)

At these visits a qualified health care practitioner listed on the site's responsibilities and delegation logs will conduct a review of organ systems and a targeted physical exam and will evaluate subjects for any new signs or symptoms that could indicate one of the AESIs as specified in the list of AESIs stored in the Investigator Site File. They will also interview the subject about recent medical history and any new diagnosis that could indicate an AESI. Medical records related to any new medical event or diagnosis will be requested, reviewed by the site staff, and recorded in the subject's source documents.

A diagnosis of an AESI will be reported in the same manner and time frame as an SAE using the VSAE form. The investigator must notify Novartis within 24 hours. The AESI diagnosis, as well as any medications taken to treat the condition, will be recorded in the subject's source documents and on the appropriate CRF.

7.1.5 Methods for Recording Adverse Events and Serious Adverse Events

All findings regarding Adverse Events must be reported on the appropriate CRF page and on the VSAE form, if applicable, which is part of the Investigator Site File. All findings in subjects experiencing AEs must be reported also in the subject's source document.

All SAEs which occur during the course of the study, whether considered to be associated with the study vaccination or not, must be reported **within 24 hours of the site becoming aware of the event** to Novartis or its designee. Specific instructions and contact details for collecting and reporting SAEs to Novartis will be provided to the investigator.

All SAEs are also to be documented on the appropriate CRF page. Any medication or other therapeutic measures used to treat the AE will be recorded on the appropriate CRF(s) in addition to the outcome of the AE.

After receipt of the initial report, representatives of Novartis or its designee will contact the investigator if it is necessary to obtain further information for assessment of the event.

All SAEs must be reported by the investigator to his/her corresponding EC and applicable regulatory authorities in accordance with institutional policy/regulatory requirements and adequate documentation of this notification must be provided to the Sponsor.

Novartis or its designee must also comply with the applicable regulatory requirement(s) related to the reporting of suspected unexpected serious adverse vaccine reactions (also known as SUSARs) to the regulatory authority(ies) and the IRB/EC. If a SUSAR or other safety signal relating to use of one of the study vaccines is reported to Novartis or its designee, the Sponsor will communicate the information to the investigator and the investigator will be responsible for submitting this information to the EC and other relevant authorities.

7.1.5.1 Post-Study Events

Any suspected SAE that occurs outside of the protocol-specified follow-up period or after the end of the study but considered to be caused by the study vaccine must be reported to Novartis or its designee. These SAEs will be processed by Novartis or its designee as during the course of the study, until 3 months after the last scheduled study visit. Instructions and contact details for collecting and reporting these suspected SAEs will be provided to the investigator.

7.1.6 Pregnancies

To ensure subjects' safety, each pregnancy in a subject after study vaccination must be reported to Novartis within 72 hours of the site learning of its occurrence. If the subject agrees to submit this information, the pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if intended duration of safety follow-up for the study has ended.

Pregnancy data must be recorded on a Pregnancy Report CRF (initial report) and Pregnancy Follow-Up CRF (outcome report).

Any pregnancy outcome meeting the definition of a SAE (see section 7.1.4) must also be reported on the VSAE Report Form.

7.1.7 Safety Laboratory Measurements

Blood and urine samples will be collected from all subjects at the Pre-vaccination Screening, at Visit 1, at Visit 3 and at Visit 6 as outlined in Time and Events Table 3. The blood safety laboratory assessments will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, liver function tests (ALT, AST), a complete blood count and C-reactive protein. The urine safety laboratory assessments will include protein, glucose and red blood cells. An additional blood and urine sample will be collected in case of a clinic Early Termination Visit as outlined in section 5.5.1.

All testing will be conducted by qualified and certified laboratories. Abnormal laboratory values will be defined following the FDA CBER Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" dated September 2007, or the institution's normal ranges if they differ from CBER guidance. Please see Appendix C, D and E for further details on the Toxicity Grading Scales according to CBER.

Retesting may be performed in case of abnormal values per guidance of the investigator. Retest results will not be captured in the CRF.

7.2 Efficacy Assessment

Efficacy measurement will not be performed as part of this study.

7.3 Immunogenicity Assessment

The measures to assess the primary and secondary immunogenicity endpoints for this study are standard, i.e., widely used and generally recognized as reliable, accurate, and relevant (able to describe the quality and extent of the immune response).

The assay's used in this study to assess the primary and immunogenicity endpoints are human serum bactericidal assay (hSBA) and ELISA specific for MenC

The hSBA is a functional measure of the ability of specific antibodies, in conjunction with human complement, to kill MenC indicator strains, and is widely used and generally recognized as the serological correlate of protection. The specific ELISA will be used to measure the induction of antibodies directed against MenC following vaccination with the study vaccines.

Blood samples (approximately 10 ml) to obtain serum for hSBA and ELISA assays will be collected at Day 1, Day 8, Day 29 and Day 181 (refer to section 3.5 for detailed specimen collection procedures).

Testing will be conducted by a Novartis or designated laboratory in a blinded manner towards the treatment group. Laboratory contact details are listed in the Protocol Ancillary Document.

All data will be captured at the laboratory and transferred via Electronic Data Transfer (EDT)

Details on all blood sample handling steps are described in the Clinical Specimen Lab Manual provided to the study site.

7.4 Exploratory Measurements

In those subjects who agree to a separate Informed Consent, additional blood samples will be collected at Day 1, Day 4, Day 8, Day 29 and Day 181 for exploratory measurements. The purpose of these exploratory measurements is to assess the systemic exposure of LHD153, to further delineate vaccine induced antigen specific immune responses and to evaluate biomarkers that may be predictive for safety and/or innate immune activation.

All exploratory measurements will be conducted by a Novartis or a designated laboratory. Laboratory contact details are listed in the Protocol Ancillary Document.

Exploratory measurements may be performed after the Clinical Study Report (CSR) has been completed, in which case these data will be submitted as an addendum to the CSR.

Systemic exposure of LHD153

Systemic exposure of LHD153 will be assessed by analyzing LHD153 blood plasma levels at Day 1 (baseline, 1, 2, 4, 8 and 24h after vaccination) and Day 4 using LC/MS/MS. Time-points for assessment of clinical exposure of LHD153 have been selected based on non-clinical data in dogs and rats.

Vaccine-induced antigen-specific immune responses

The frequency of B cells specific for MenC polysaccharide and CRM_{197} will be determined by enzyme-linked immunosorbent spot (ELISPOT) at Day 1, Day 8, Day 29 and Day 181 in order to evaluate the baseline specific B-cell frequency (Day 1), the peak of plasmablast responses (Day 8), the peak of B cell memory responses (Day 29), and the persistence of memory B cell responses (Day 181).

Subsequently, the diversity of the antigen specific B-cell repertoire as well as the specific antibody functionality will be analyzed in a selected subset of subjects. The selection of the subset will be based on the most pronounced response to the study vaccines when compared to baseline as determined by the primary and secondary immunogenicity assessment.

The diversity of the elicited B-cell receptors will be assessed through sequence analysis of complementary DNA (cDNA) generated from immunoglobulin (Ig) messenger RNA (mRNA). The Ig cDNAs will be analyzed from antigen-specific B cells obtained at Day 1, Day 29 and/or Day 181 and plasmablasts isolated at Day 8. The analysis of the B-cell receptor diversity does not have the intent nor the capability to identify or rule out any genetic modifications in the RNA or DNA that are presumably linked to disease or predisposition to disease.

To evaluate the functionality specific antibodies induced by the study vaccines, biochemical and cell-based assays will be performed on a selected subset of serology samples collected for the assessment of the primary and secondary immunogenicity endpoints at Day 1, Day 8, Day 29 and Day 181. The evaluation of antigen specific antibody functionality includes determination of the antibody isotype and the antibody glycosylation state. Furthermore, the ability of the MenC-specific antibodies to fix complement, to promote antibody-dependent cell mediated cytoxicity (ADCC), to induce phagocytosis and to activate FcR+ cells in vitro will be assessed. If the quantity of serum available for this specific exploratory objective is limited, assessments of isotype and glycosylation state will be prioritized over the other assessments.

The frequency of T cells specific for the CRM_{197} protein at baseline (Day 1), at Day 8 and at Day 29 after vaccination with the study vaccines will be determined by FACS analysis using intracellular staining with a panel of cytokines and surface markers to identify cell populations.

Early Markers for Safety and Innate immune activation

The evaluation of potential biomarkers of safety and innate immune activation will be performed on blood specimens collected at Day 1 (baseline, 6h and 24h after vaccination) and Day 4.

The vaccine-induced production of inflammatory cytokines and chemokines will be monitored on serum samples using a commercially available electrochemoluminescence assay for a panel of pro-inflammatory cytokines and chemokines, including Eotaxin, Eotaxin-3, GM-CSF, IFN-g, IL-1a, IL-1b, IL-10, IL-12 p70, IL-12/IL-23p40, IL-13,

IL15, IL-16, IL-17A, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-8 (HA), IP-10, MCP-1, MCP-4, MDC, MIP-1a, MIP-1b, TARC, TNF-a, TNF-b, VEGF.

The vaccine-induced expression of genes and gene families will be monitored on whole blood samples using of RNA microarrays by existing technologies. The RNA micro array analysis does not have the intent nor the capability to identify or rule out any genetic modifications in the RNA or DNA that are presumably linked to disease or predisposition to disease.

8.0 STATISTICAL CONSIDERATIONS

8.1 Endpoints

8.1.1 Primary Endpoint(s)

8.1.1.1 Primary Safety Endpoint(s)

The measures for assessing safety and tolerability (by vaccine group within each cohort and by LHD153R adjuvant dosage group overall) are as follows:

- The frequency and percentage of subjects with solicited local and systemic AEs through Day 14. Time intervals after vaccination that will be summarized are:30 minutes post-vaccination, Days 1-4 (without 30 minutes), Days 5-8, Days 8-14, Days 1-8 (without 30 minutes) and Days 1-14 (without 30 minutes).
- The frequency and percentage of subjects with any unsolicited AEs from the day of vaccination (Day 1) to Day 14.
- The frequency and percentage of subjects with SAEs, medically attended AEs, AEs leading to study withdrawal, NOCDs, AESIs for the following time periods: day of signed informed consent until study completion (Day 366), day of vaccination (Day 1) to Day 29, and Day 29 to study completion (Day 366).
- The absolute values and changes in hematology, chemistry, and urinalysis parameters (see section 7.1.7).
- The frequency and percentage of subjects with abnormal laboratory parameter values

as classified by investigator normal ranges (low, normal, high) and as classified by CBER toxicity grading scales, when available. **8.1.1.2 Primary Efficacy Endpoint(s)**

Not applicable.

8.1.1.3 Primary Immunogenicity Endpoint(s)

The primary immunogenicity endpoints are the GMTs measured by hSBA directed against MenC from samples collected on Day 1 (baseline, before vaccination) and Day 29 as well as the GMR of the titers (Day 29 / Day 1).

8.1.2 Secondary Endpoint(s) 8.1.2.1

Secondary Safety Endpoint(s)

Not applicable.

8.1.2.2 Secondary Efficacy Endpoint(s)

Not applicable.

8.1.2.3 Secondary Immunogenicity Endpoint(s)

The secondary immunogenicity endpoints are:

- GMTs and corresponding GMRs measured by hSBA directed against MenC for samples collected at Day 8 and Day181.
- Percentage of subjects with hSBA seroresponse at Days 8, 29, and 181. Seroresponse is defined as a post vaccination hSBA ≥8 for subjects with a baseline hSBA <4 or have an increase of at least 4 times the baseline hSBA level for subjects with prevaccination hSBA ≥4.
- Antibody geometric mean concentrations (GMCs) against MenC measured by ELISA for samples collected on Days 1 (baseline, prior to vaccination), 8, 29, and 181.
- The percentage of subjects with at least a 4-fold increase in antibody concentrations to MenC as measured by ELISA on Day 8, 29, and 181 relative to baseline (Day 1).

8.1.3 Exploratory Endpoint(s)

The exploratory endpoints are based on results of testing which may not be performed until after the study report has been finalized and will be further refined prior to testing. They include the following:

- Serum concentration of LHD153 at Day 1 baseline (prior to vaccination), Day 1 (1h , 2h, 4h, 8h, and 24h after vaccination), Day 4 by LC-MS/MS.

- Frequency of MenC polysaccharide-specific and CRM_{197}-specific B cells at Day 1 (baseline), Day 8, Day 29, and Day 181 by ELISPOT.
- Diversity of MenC polysaccharide-specific B-cell repertoire at Day 1 (baseline), Day 8, Day 29, and Day 181 by immunoglobulin cDNA sequencing.
- Functionality of antigen specific antibodies will be assessed at Day 1 (baseline), Day 8, Day 29, and Day 181 by analysis of immunoglobulin isotype, glycosylation state and their ability to fix complement, to promote antibody-dependent cell mediated cytoxicity, to induce phagocytosis and to activate FcR+ cells. If the quantity of serum available for this specific exploratory objective is limited, assessments of immunoglobulin isotype and glycosylation state will be prioritized over the other assessments.
- Frequency and quality of T cells specific for CRM_{197} at Day 1 (baseline), Day 8, and Day 29 by fluorescence activated cell sorting (FACS) analysis using intracellular staining with a wide panel of cytokines and surface markers to identify cell populations.
- Serum concentrations of a panel of 30 chemokines and cytokines at Day 1 baseline (prior to vaccination), Day 1 (6h and 24h after vaccination), Day 4, and Day 8 by multiplex Electro-chemo-luminescence based assay.
- Gene expression profile in whole blood at Day 1 baseline (prior to vaccination), Day 1 (6h and 24h after vaccination), Day 4, and Day 8 by RNA micro array analysis.

8.2 Success Criteria

The study has no formal statistical hypotheses and will not be declared positive or negative according to given rules. The selection of an appropriate LHD153R adjuvant dosage for future studies will be determined by the joint evaluation of the immunogenicity and safety profiles of each dosage group. **8.2.1 Success Criteria for Primary Objective(s)** Not applicable.

8.2.2 Success Criteria for Secondary Objective(s)

Not applicable.

8.3 Analysis Sets

8.3.1 All Enrolled Set

All screened subjects who provide informed consent and provide demographic and/or baseline screening assessments, regardless of the subject's randomization and treatment status in the study and received a Subject ID.

8.3.2 All Exposed Set

All subjects in the enrolled set who receive a study vaccination.

8.3.3 Safety Set

Safety Set (solicited adverse events and other solicited reactions)

All subjects in the Exposed Set who:

- Provide post vaccination reactogenicity data.

Safety Set (unsolicited adverse events)

All subjects in the Exposed Set who:

- Have post-vaccination unsolicited adverse event records.

Safety Set (overall)

All subjects in the Exposed Set who:

- Have either post-vaccination adverse event or reactogenicity records.

Subjects will be analyzed as "treated" (i.e., according to the vaccine a subject received, rather than the vaccine to which the subject may have been randomized).

8.3.4 Full Analysis Set (FAS) Efficacy/Immunogenicity Set

All subjects in the Enrolled Set who:

- Receive a study vaccination AND provide efficacy/immunogenicity data at relevant time points.

FAS sets will be analyzed "as randomized" (i.e., according to the vaccine a subject was designated to receive, which may be different from the vaccine the subject actually received).

8.3.5 Per Protocol (PP) Set Efficacy/Immunogenicity Set

All subjects in the FAS efficacy/immunogenicity set who:

- Are not excluded due to reasons (see section 8.3.8) defined prior to unblinding or analysis.

PPS are subsets of FAS and should always be defined even if the objectives do not require it.

Examples for subjects excluded due to other reasons than protocol deviations are:

- Subjects who withdrew informed consent.
- Premature withdrawal due to an adverse event.

Exclusions need to be considered by objective/time point, i.e., sometimes not all data of a subject but only part of the subject's data will be removed from the PPS analysis.

8.3.6 Other Analysis Sets

All subjects in the Enrolled Set who consent to additional blood draws, receive a study vaccination AND provide exploratory assay data at relevant time points will be included in an exploratory assay subset.

8.3.7 Subgroups

Selected immunogenicity analyses may be provided based on seropositivity status at baseline.

8.3.8 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. A protocol deviation may be a reason to remove data from an analysis set at the time of analysis. Reportable protocol deviations will be defined as exclusionary from the analysis according to protocol objectives and endpoints, which will be specified in the Statistical Analysis Plan. In some cases exclusion of data may be due to a reason other than a protocol deviation, e.g. early termination.

8.4 Statistical Analysis Plan

This section provides a summary of the statistical methodology to be used. A more detailed description of analysis methods will be provided in a separate Statistical Analysis Plan which may also include additional exploratory analyses not explicitly mentioned in the following sections.

8.4.1 Analysis of Demographic and Baseline Characteristics

Descriptive statistics (number of non-missing observations, mean, standard deviation, median, minimum and maximum) for age, height and weight at enrolment will be calculated overall and by vaccine group and LHD153R adjuvant dosage.

Distributions of subjects by sex and ethnic origin will be summarized overall and by vaccine group and LHD153R adjuvant dosage.

8.4.2 Analysis of Primary Objective(s)

8.4.2.1 Analysis of Primary Safety Objective(s)

Safety of the study vaccines will be assessed in all subjects in terms of the frequency and percentage of reported AEs as well as by changes in clinical laboratory values.

8.4.2.1.1 Analysis of Extent of Exposure

The frequency and percentage of subjects with vaccinations will be summarized by vaccine group and LHD153R adjuvant dosage, by cohort and overall, for the Enrolled Set.

8.4.2.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events

All solicited adverse events will be summarized according to defined severity grading scales. Use of medication to prevent/treat fever will be summarized according to frequencies and percentages reporting “Yes” and “No”.

Frequencies and percentages of subjects experiencing each adverse event will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic adverse event overall and at each time point will also be presented.

Post-vaccination solicited adverse events reported from Day 1 to Day 14 will be summarized for the intervals Day 1-4 (without 30 minutes), Day 5-8, Day 1-8 (without 30 minutes), Day 8-14 and Day 1-14 (without 30 minutes) by maximal severity and by vaccine group and LHD153R adjuvant. The severity of solicited local adverse events, including injection-site erythema, swelling and induration will be summarized according to categories based on linear measurement: 25-50 mm, 51-100 mm, > 100 mm.

Injection site pain and systemic reactions (except fever) occurring up to Day 14 will be summarized according to “mild”, “moderate” or “severe”.

Each solicited local and systemic adverse event will also be further summarized as “none” versus “any”.

Implausible measurements (for further definition see Statistical Analysis Plan) will be left out of the analysis.

Use of antipyretics and analgesics will be summarized by frequency by type of use (prophylactic versus treatment) and percentage of subjects reporting use. The influence of antipyretics and analgesics use on the occurrence of specific adverse events (e.g., fever, pain) will be assessed.

Body temperature will be summarized by 0.5 °C and 1.0 °C increments from 36.0 °C up to ≥40 °C.

8.4.2.1.3 Analysis of Unsolicited Adverse Events

This analysis applies to all adverse events occurring during the study, judged either as probably related, possibly related, or not related to vaccination by the investigator, recorded in the CRF, with a start date on or after the date of first vaccination. AE starting prior to the first vaccination will only be listed. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class.

All reported adverse events, as well as adverse events judged by the investigator as at least possibly related to study vaccine, will be summarized according to system organ class and preferred term within system organ class. These summaries will be presented by vaccination group and LHD153R adjuvant dosage for each cohort and by interval of study observation. When an adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted.

Separate summaries will be produced for the following categories:

- Serious adverse events.
- Adverse events that are possibly or probably related to vaccine.
- Adverse events of special interest.
- New onset of chronic disease.
- Adverse event leading to withdrawal.
- Adverse events leading to a medically attended visit.

- Adverse event by data source.

Data listings of all adverse events will be provided by subject. In addition, adverse events in the categories above will be provided as listed data.

8.4.2.1.4 Analysis of Safety Laboratory Values

The investigator must review all safety laboratory results (see Section 7.1.7). Abnormal laboratory values and clinically significant changes in values from pre-vaccination (Screening Visit) will be assessed, using medical judgment, based on the FDA CBER Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" dated September 2007, or the institution's normal ranges if they differ from CBER guidance. Please see Appendix C, D and E for further details.

The following information will be provided:

- Change in absolute laboratory value from pre-vaccination (Screening Visit) and Day 1 (Visit 1) baseline to Day 8 (Visit 3) and Day 29 (Visit 6) after vaccination.
- The classification of laboratory values and/or their changes from pre-vaccination according to the CBER toxicity grading scale.
- 3 x 3 shift tables by visit using the categorization of laboratory values according to institutional normal reference ranges (below, within, above).

8.4.2.2 Analysis of Primary Efficacy Objective(s)

Not applicable.

8.4.2.3 Analysis of Primary Immunogenicity Objective(s)

8.4.2.3.1 Statistical Hypotheses

There are no statistical hypotheses associated with the primary immunogenicity objectives. All analyses are descriptive.

8.4.2.3.2 Analysis Sets

The primary immunogenicity analyses will be based on the per-protocol set (PPS) at Day 29. The primary analyses will be repeated using the Full Analysis Set (FAS) as a measure of the sensitivity/robustness of the results (further details are given in section 8.3).

8.4.2.3.3 Statistical Methods

Before any statistical analysis that assumes normally distributed observations, antibody titers will be $\log_{10}$-transformed. Individual titers below the limit of quantitation (LLQ) will be set to half that limit.

Geometric Mean Titers

The logarithmically (base 10) transformed antibody titers will be modeled using an analysis of covariance (ANCOVA) model with a qualitative factor for LHD153R adjuvant dosage (0 [for unadjuvanted MenC], 12.5, 25, 50 or 100 µg) and log (base 10) pre-vaccination titer as a covariate. The adjusted GMT and the two-sided, 95%, confidence intervals (CIs) of the GMT will be calculated based on this model as will the ratio of GMTs and corresponding CIs. The adjusted GMT and two-sided 95% CIs will be constructed by exponentiation (base 10) of the least square means of the logarithmically transformed (base 10) antibody titer. The ratio of GMTs (LHD153R adjuvant dosage minus Men C), and corresponding two-sided 95% CIs, will be constructed by exponentiation (base 10) of the least square differences obtained from this model. The model can be written as:

$$\log_{10}(y_{ik}) = \mu + \alpha_i + \beta x_{ik} + \varepsilon_{ik}$$

where μ represents a common overall mean, α_i represents the adjuvant dose group i effect, β represents the common slope for the log10 pre-vaccination titer, x_{ik} for subject k in adjuvant dose group I, and ε_{ik} represents random error for subject k in adjuvant dose group i.

Geometric Mean Ratios

The logarithmically (base 10) transformed within subject ratio of antibody titers (Day 29 / pre-vaccination) will be modeled using an analysis of variance model with a qualitative factor for LHD153R adjuvant dosage (0 [for non-LHD153R adjuvanted MenC], 12.5, 25, 50 or 100 µg). The adjusted GMR and the two-sided, 95% CIs of the GMR will be calculated based on this model. The model can be written as:

$$\log_{10}(y_{ik}) = \mu + \alpha_i + \varepsilon_{ik}$$

where μ represents a common overall mean, α_i represents the adjuvant dose group i effect and ε_{ik} represents random error for subject k in adjuvant dose group i.

Handling of missing values

For immunogenicity data, it may be reasonable to consider missing immunogenicity values as missing completely at random (MCAR), i.e., not informative. Therefore, the primary analysis will comprise a complete case analysis only, without introducing any bias. Imputation methods will not be used.

8.4.3 Analysis of Secondary Objective(s) 8.4.3.1

Analysis of Secondary Safety Objective(s) Not

applicable.

8.4.3.2 Analysis of Secondary Efficacy Objective(s)

Not applicable.

8.4.3.3 Analysis of Secondary Immunogenicity Objective(s)

8.4.3.3.1 Statistical Hypotheses

There are no statistical hypotheses associated with the secondary immunogenicity objectives. All analyses are descriptive.

8.4.3.3.2 Analysis Sets

The secondary immunogenicity analyses will be based on the PPS (further details are given in section 8.3) or the appropriate subset of subjects.

8.4.3.3.3 Statistical Methods

The secondary immunogenicity endpoints are:

- GMTs and corresponding GMRs measured by hSBA directed against MenC for samples collected at Day 8 and Day181.
- Percentage of subjects with hSBA seroresponse at Days 8, 29, and 181. seroresponse is defined as a post vaccination hSBA ≥8 for subjects with a baseline hSBA <4 or have an increase of at least 4 times the baseline hSBA level for subjects with prevaccination hSBA ≥4.
- Antibody geometric mean concentrations (GMCs) against MenC measured by ELISA for samples collected on Days 1 (baseline, prior to vaccination), 8, 29, and 181.

- The percentage of subjects with at least a 4-fold increase in antibody concentrations to MenC as measured by ELISA on Day 8, 29, and 181 relative to baseline (Day 1).

The GMTs for samples collected at Day 8 and Day 181 as well as the GMCs for samples collected at Day 1, Day 8, Day 29, and Day 181 will be analyzed using the same approach as for the primary immunogenicity endpoint.

The remaining immunogenicity endpoints are based on subjects meeting criteria for seroconversion or achieving a certain threshold value. These endpoints will be summarized using frequencies and percentages by LHD153R adjuvant dosage (0 [for non-LHD153R adjuvanted MenC], 12.5, 25, 50 or 100 µg). Two-sided 95% ClopperPearson CIs will also be provided for percentages. For analyses of seroconversion, separate summaries may be provided based on seropositivity status at baseline.

8.4.4 Analysis of Exploratory Objectives

Testing and analyses of exploratory endpoints may be performed after the Clinical Study Report (CSR) has been completed, in which case these data will be submitted as an addendum to the CSR.

In general, concentration and titer results will be summarized for each LHD153R adjuvant dosage group using geometric means and associated 2-sided 95% confidence intervals; and, categorical data will be summarized using frequencies and percentages, with corresponding two-sided, 95% confidence intervals.

8.5 Sample Size and Power Considerations of Primary Objectives

Sample size is not driven by statistical assumptions for formal hypothesis testing, but was based on the safety objective for the study. The table below provides the probability for various combinations of sample size (N) and presumed true frequency of a given event within an individual vaccine group

Frequency of Event	Probability to Observe at Least 1 Subject with a Given Event For Various Choices of N			
	4	8	12	16
0.05	0.1855	0.3366	0.4596	0.5599
0.10	0.3439	0.5695	0.7176	0.8147
0.15	0.4780	0.7275	0.8577	0.9257

0.20	0.5904	0.8322	0.9313	0.9718
0.30	0.8250	0.9423	0.9862	0.9967
0.40	0.8704	0.9832	0.9978	0.9997

The proposed combinations of sample sizes within each cohort are 4 aluminium hydroxide adjuvanted MenC-CRM$_{197}$ and 16 MenC-CRM$_{197}$ plus an assigned-level of LHD153R adsorbed to aluminium hydroxide. If all four cohorts are fully enrolled, there will be 16 subjects receiving aluminium hydroxide adjuvanted MenC-CRM$_{197}$.

With 16 subjects, events which occur at a frequency of 15% or more will be detected with at least 90% probability; and, events which occur at a frequency of 10% or more will be detected with 81% probability. With 4 subjects, events which occur at a frequency of 30% or more will be detected with at least 80% probability. Intermediate values of 8 and 12 are provided to correspond to sample sizes in the MenC- CRM$_{197}$ after cohort 2 and cohort 3 are fully enrolled.

8.6 Interim Analysis

The DMC will be reviewing the accumulating safety data from the study in order to continue enrollment of subjects within a cohort and whether to enroll subjects into the next cohort.

In addition to these periodic reviews, there will be a safety and immunogenicity interim analysis for the selection of an LHD153R adjuvant dosage based on the data collected through Day 29 from subjects enrolled in all cohorts. This analysis will be performed by personnel not involved in study decisions. The results will be unblinded at the group level thereby preserving the blind for individual subjects. No adjustment to the overall alpha will be performed as the data collected subsequent to this analysis involve secondary and exploratory endpoints.

9.0 SOURCE DOCUMENTATION, STUDY MONITORING AND AUDITING

Study monitoring and auditing will be standardized and performed in accordance with the Sponsor's or delegated contract research organization's (CRO) standard operating procedures and applicable regulatory requirements (e.g., FDA, EMA, and ICH guidelines).

Prior to enrolment of the first study subject, Novartis or delegate will train investigators and/or their study staff on the study protocol, all applicable study procedures, documentation practices and all electronic systems. CRFs must be completed for each enrolled subject (see section 8.3.1 for definition of enrolled subject). Documentation of screened but not enrolled subjects must be maintained at the site and made available for review by the site monitor.

9.1 Source Documentation

Prior to the start of the study, the site staff participating in the study conduct will be instructed on what documents will be required for review as source documents. The kinds of documents that will serve as source documents will be agreed between Sponsor or delegate and investigator and designees and specified in the SDA/Source Data Verification Form prior to subject enrolment.

In addition, source documentation **must** include all of the following: subject identification (on each page), eligibility and participation, proper informed consent procedures, dates of visits, adherence to protocol procedures, adequate reporting and follow-up of adverse events, documentation of prior/concomitant medication/vaccines, study vaccine receipt/dispensing/return records, study vaccine administration information, any data collected by a telephone conversation with the subject and date of completion and reason.

The subject must also allow access to the subject's medical records. Each subject must be informed of this prior to the start of the study and consent for access to medical records may be required in accordance with local regulations.

All safety data reported by subjects must be written down in source documents. If there are multiple sources of information (e.g., Subject Diary, verbal report of the subject, telephone contact details, medical chart) supporting the diagnosis of an adverse event, these sources must be identified in the source documents, discrepancies between sources clarified, the ultimate diagnosis must be justified and written in the source documents, and this diagnosis must be captured in the appropriate CRF page. The CRF must also

capture which source(s) of information were used to determine the adverse event (e.g., subject recall, medical chart, Subject Diary).

9.2 Study Monitoring, Auditing and Source Data Verification

Prior to enrolment of the first study subject, Novartis or its designee (e.g., a CRO) will develop a Monitoring Plan to specify how centralized and/or on-site monitoring, including clinical specimens reconciliation, will be performed for the study. Study progress will be monitored as frequently as necessary to ensure:

- that the rights and well-being of human subjects are protected,
- the reported study data are accurate, complete, and verifiable from the source documents and
- the conduct of the study is in compliance with the current approved protocol/amendment(s), GCP and applicable regulatory requirements.

Contact details for the team involved in study monitoring will be provided to the investigator. Study data recorded on CRFs will be verified by checking the CRF entries against source documents in order to ensure data completeness and accuracy as required by study protocol.

Additional documents such as the investigator site file, pharmacy records, and informed consent documentation must also be available for review if requested. Arrangements for monitoring visits will be made in advance in accordance with the monitoring plan, except in case of emergency.

The investigator and/or site staff must make source documents of subjects enrolled in this study available for inspection at the time of each monitoring visit and Sponsor audits, when applicable. These documents must also be available for inspection, verification and copying, as required by regulations, by officials of the regulatory health authorities (e.g., FDA, EMA and others) and/or ECs/IRBs. The investigator and study site staff must comply with applicable privacy, data protection and medical confidentiality laws for use and disclosure of information related to the study and enrolled subjects.

10.0 DATA MANAGEMENT

10.1 Data Entry and Management

In this study, all clinical data (including, but not limited to, AE/SAEs, concomitant medications, medical history, and physical assessments), safety data, and immunogenicity data will be entered into an EDC system, which is compliant with Title 21 Part 11

policies of the Code of Federal Regulations (FDA, 1997). The data system includes password protection and internal quality checks. The EDC system will be designed and validated by the Sponsor prior to activation for data entry by sites. The investigator or designated delegate must review data entered and electronically sign the CRFs to verify their accuracy.

Access to the EDC system for data entry or review will require training and distinct individual access code assignments to those site staff members who will be entering study data and those involved in study oversight who may review study data. Data are collected within the EDC system, to which the Sponsor and site monitors have exclusively "read only" access.

Paper CRFs will be provided for each pregnant subject by the Sponsor. All appropriate pregnant subject data collected will be recorded on this form. One copy must be retained by the investigator, and all other copies (including the original copy) will be returned as directed by the Sponsor. Instructions on how to complete this form will be provided to the investigator.

10.2 Data Clarification

As part of the conduct of the trial, the Sponsor may have questions about the data entered by the site, referred to as queries. The monitors and the Sponsor are the only parties that can generate a query. All corrections and clarifications will be entered into the EDC system and will be identified by the person entering the information, the reason for the change, as well as the time of the changes made. If changes are made to a previously and electronically signed CRF, the investigator must confirm and endorse the changes

10.3 Data Protection

Novartis respects the subjects' rights to privacy and will ensure the confidentiality of their medical information in accordance with all applicable laws and regulations.

The Sponsor as Data Controller according to the European Directive on the protection of individuals with regard to the processing of personal data and on the free movement of such data (95/46/EC) confirms herewith compliance to Directive 95/46/EC in all stages of Data Management.

11.0 RECORD RETENTION

Investigators must retain all study records required by Novartis and by the applicable regulations in a secure and safe facility. The investigator must consult a Novartis representative before disposal of any study records, and must notify the Sponsor of any change in the location, disposition, or custody of the study files. Essential documents must be retained for 15 years. “Essential documents” are defined as documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. These documents should be retained for a longer period, however, if required by the applicable national regulatory or institutional requirements.

These principles of record retention will also be applied to the storage of laboratory samples, provided that the integrity of the stored sample permits testing.

12.0 USE OF INFORMATION AND PUBLICATION

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov, and in compliance with current regulations.

Novartis also assures that key results of this clinical study will be posted in a publicly accessible database within the required time-frame from the End of Study as defined in section 3.9.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Novartis must be notified of any intent to publish data collected from the study and prior approval from Novartis must be obtained prior to submission for publication.

13.0 ETHICS

13.1 Regulatory and Ethical Compliance

The study will be conducted in compliance with the protocol, GCP and applicable regulatory requirement(s).

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, European Directive 2001/20/EC, Novartis codes on protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki (European Council 2001, US Code of Federal Regulations, ICH 1997).

13.2 Informed Consent Procedures

Eligible subjects may only be included in the study after providing written informed consent or assent, as described in section 5.1.1. Before the start of the study, the investigator will have the informed consent and any other materials that will be provided to the subjects reviewed and approved by the IRB/EC. This review and approval will be documented and stored with other study documents. The investigator or designee must fully inform the subject or legal guardian of all pertinent aspects of the study. A copy of the written informed consent will be given to the subject or the designee. The subject/designee must be allowed ample time to ask about the details of the study and to make a decision as to whether or not to participate in the study. The subject and/or legal guardian(s) **must** sign the consent form indicating their agreement to participate in the study before any study-related procedures are conducted. The informed consent process may be conducted up to 23 days prior to vaccination on Day 1. If the subject is unable to read and write, a witness must be present during the informed consent discussion and at the time of informed consent signature.

Prior to the start of the study, Novartis will provide to investigators a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/EC and a copy of the approved version must be provided to Novartis after IRB/EC approval.

Women of childbearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception

requirements indicated in the protocol for the duration of the study. In case of doubt on the ability of a subject to adhere to these requirements, that subject should not be allowed in the study

13.3 Responsibilities of the Investigator and IRB/EC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB/EC before study start. Properly constituted IRB/EC is defined in ICH Guideline for Good Clinical Practice E6 (R1), Section 3 (ICH, 1997). A signed and dated statement that the protocol and informed consent have been approved by the IRB/EC must be given to Novartis before study initiation. Prior to study start and at any time the protocol is amended during study conduct, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/ECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

The investigator also responsible for the following:

- Maintaining a list of appropriately qualified persons to whom the investigator has delegated significant study-related duties.
- Demonstrating the capability of recruiting the required number of suitable subjects within the recruitment period.
- Demonstrating sufficient time and staffing to properly conduct and complete the study within the agreed study period.
- Ensuring that all persons assisting with the study are adequately informed about the protocol, the investigational product(s), and their study-related duties and functions
- Ensuring that appropriately trained health care professionals are responsible for all study-related medical decisions and for ensuring appropriate medical care of subjects experiencing any adverse event related to the study.
- If permission to do so is given by the subject, ensuring that the subject's primary healthcare provider is informed of the subject's participation in the study.

The investigator should not implement any deviation from, or changes of the protocol without agreement by the Sponsor and prior review and documented approval/favourable

opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone number(s)). In addition, the investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to study subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

(a) to the IRB/IEC for review and approval/favourable opinion,

(b) to the Sponsor for agreement and, if required,

(c) to the regulatory authority(ies).

13.4 Protocol Amendments

An amendment is a written description of change(s) to or formal clarification of a study protocol which may impact on the conduct of the clinical study, potential benefit of the clinical study, or may affect subject safety, including changes of study objectives, study design, subject population, sample sizes, study procedures, or significant administrative aspects. An administrative change of a study protocol is a minor correction or clarification that has no significant impact on the way the clinical study is to be conducted and no effect on subject safety (e.g., change of telephone number(s), logistical changes). Protocol amendments must be approved by Novartis, health authorities where required, and the IRB/EC. In cases when the amendment is required in order to protect the subject safety, the amendment can be implemented prior to IRB/EC approval. Notwithstanding, the need for formal approval of a protocol amendment, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action, the IRB/EC at the study site, and, if required by local regulations, the relevant health authority should be informed within 10 working days.

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APPENDIX A: GRADING SCALES FOR SOLICITED LOCAL ADVERSE EVENTS*

(Adapted from CBER 2007b)

Adverse event Following Administration of Injectable Product	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Pain	present but does not interfere with activity	interferes with activity	prevents daily activity
Induration / Swelling / Erythema	25 – 50 mm	51 – 100 mm	> 100 mm

*This toxicity grading scale is adapted from CBER 2007 to enable ease of reporting by Subjects in the source documents for 'patient reported' solicited adverse events. This toxicity grading scale is a Novartis standard that is used for patient reporting. 'Grade 4' is not listed here but will be defined in the Statistical Analysis Plan as necessary.

APPENDIX B: GRADING SCALES FOR SOLICITED SYSTEMIC ADVERSE EVENTS*

(Adapted from CBER 2007b)

Systemic Adverse event		Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Fever	**°C**	38.0 – 38.4	38.5 – 38.9	39.0 – 40
	°F	100.4 – 101.1	101.2 - 102	102.1 - 104
Chills		present but does not interfere with activity	interferes with activity	prevents daily activity
Loss of Appetite		Loss of appetite without decreased oral intake	decreased oral intake without weight loss	decreased oral intake with weight loss
Nausea		Nausea present but not interfering with oral intake	Nausea leading to decreased oral intake	Nausea leading to minimal to no oral intake
Vomiting		1-2 episodes/24 hours	>2 episodes/24 hours	requires outpatient hydratation
Diarrhea		2-3 loose stools /24 hours	4-5 loose stools /24 hours	6 or more watery stools /24 hours or requires outpatient IV hydration
Generalized Myalgia		present but does not interfere with activity	interferes with activity	prevents daily activity
Generalized Arthralgia		present but does not interfere with activity	interferes with activity	prevents daily activity
Headache		present but does not interfere with activity	interferes with activity	prevents daily activity
Fatigue		present but does not interfere with activity	interferes with activity	prevents daily activity
Generalized Rash		localized area of the skin (1 extremity only)	moderate area of the skin (2 or more body regions without whole body involvement)	most of the skin
Urticaria		localized area of the skin (1 extremity only)	moderate area of the skin (2 or more body regions without whole body involvement)	most of the skin

*This toxicity grading scale is adapted from CBER 2007b to enable ease of reporting by Subjects in the source documents for 'patient reported' solicited adverse events. This toxicity grading scale is a Novartis

standard that is used for patient reporting. 'Grade 4' is not listed here but will be defined in the statistical analysis plan as necessary

APPENDIX C: TOXICITY SCALES FOR LABORATORY ABNORMALITIES (SERUM CLINICAL CHEMISTRY)

Serum*,**	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)***
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN

*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

**Laboratory values that fall in the normal range may be assigned a category of "Grade 0."

***The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value. "ULN" = the upper limit of the normal range.

APPENDIX D: TOXICITY SCALES FOR LABORATORY ABNORMALITIES (HEMATOLOGY)

Hematology*,**	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0

Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Platelets Decreased cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000

*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

**Laboratory values that fall in the normal range may be assigned a category of "Grade 0."

APPENDIX E: TOXICITY SCALES FOR LABORATORY ABNORMALITIES (URINE)

Urine*,**	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

**Laboratory values that fall in the normal range may be assigned a category of "Grade 0."

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CLINICAL STUDY PROTOCOL SPONSOR SIGNATURE PAGE

Study Number: V132_01EXP

Protocol Title: A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine in Healthy Adults (18-45 years of age)

Date of Final Issued Protocol and Version: 17 DEC 2014, Version 3

Signature page for sponsor's representative

The following sponsor's representative has reviewed and approved the protocol entitled "A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine in Healthy Adults (18-45 years of age)." In addition, this study protocol has been approved by the Novartis Vaccines and Diagnostics Protocol Review Committee and received an electronic approval signature on 17 DEC 2014.

17/DEC/14

....

Cluster Physician, Novartis Vaccines and Diagnostics — Date, DD MMM YY

.....

Printed Name of Cluster Physician, Novartis Vaccines and Diagnostics

PPD

CLINICAL STUDY PROTOCOL AMENDMENT

Study Number: V132_01EXP

Protocol Title: A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine in Healthy Adults (18-45 years of age)

Amendment Number 3

Revised Protocol version 4.0 issued on 18 JUN 2015

The present amendment reflects changes to the Protocol version 3.0 issued on 17DEC14

DESCRIPTION OF CHANGE(S) AND RATIONALE:

CHANGE	LOCATION(S) OF CHANGE	RATIONALE FOR CHANGE
Change in Sponsor name	Throughout the entire document	Company transition from Novartis Vaccines to GSK Vaccines
Addition of one Blood Draw and one Urine sample for Safety Laboratory assessment at 24 h after vaccination.	Synopsis (Page 12) Times and Events Table 3 (Page 19) Section 3.1 'Overview of Study Design' (Page 31) Section 3.5 'Collection of Clinical Specimens' (Pages 35 and 36) Section 5.2.5 'PostVaccination Procedures' (Page 48) Section 7.1.7 'Safety Laboratory Measurements' (Page 70 and 71)	Alignment with Early Clinical Research Experience with legacy GSK Adjuvant System (AS) platform. Transient CRPlevel increase has been observed at 24h with TLR4L (MPL) containing AS.

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CHANGE	LOCATION(S) OF CHANGE	RATIONALE FOR CHANGE
Addition of Exploratory Endpoint #8 'Number and Activation Status of myeloid and lymphoid cell populations at Day 1, Day 4 and Day 8'	Synopsis (Page 16) Times and Events Table 3 (Page 20) Section 3.5 'Collection of Clinical Specimens' (Pages 34-36) Section 7.4 'Exploratory Measurements' (Page 73) Section 8.1.3 'Exploratory Endpoints' (Page 76)	Alignment with Early Clinical Research Experience with legacy GSK AS platform. Vaccine adjuvant-induced changes in innate immune cell populations/activation state have been observed at 24h and 72h post vaccination with TLR4L (MPL) containing AS.
Changed one of the timepoints (i.e. 18h instead of 20h post-vaccination) for Body Temperature assessments in first 24h after vaccination	Times and Events Table 3 (Page 20) Section 5.2.5 'PostVaccination Procedures' (Page 48)	Alignment with Early Clinical Research Experience with legacy GSK AS platform. Transient rise in bodytemperature has been observed with TLR4L (MPL) containing AS that peaked at 18h.

Increased blood volume for LHD153 systemic exposure assay (PK analysis) from 2 mL to 3 mL	Times and Events Table 3 (Page 20) Section 3.5 'Collection of Clinical Specimens' (Pages 34-36)	Ensure sufficient plasma can be recovered for preparing 4 aliquots: 1 aliquot for the assay, 2 aliquots for potential retests and 1 back-up aliquot.

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CLINICAL STUDY PROTOCOL V132_01EXP Version 4

A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine in Healthy Adults (18-45 years of age)

EUDRACT No. 2014-002430-31

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PROTOCOL SYNOPSIS V132_01EXP

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
GlaxoSmithKline Biologicals S.A.	V132_01EXP	MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and Meningococcal C-CRM$_{197}$ Conjugate Vaccine
Title of Study: A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine in Healthy Adults (18-45 years of age)		
Study Period: Approximately 12 months for each subject		**Clinical Phase:** Phase 1

Background and Rationale:

Neisseria meningitidis (*N. meningitides*)serogroup C (MenC) is one of the major serogroups causing invasive meningococcocal disease. Case fatality in Germany has ranged between 6% and 8% between 1999 and 2006, and has remained generally consistent across the different European countries, varying between 6-11%, with the case fatality rate being notably higher for serogroup C disease than for serogroup B. The safety and immunogenicity of the GSK Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) has been confirmed through years of commercial use. For children over the age of 12 months, for adolescents and for adults a single dose is recommended. For infants between 2 and 12 months of age, the recommended schedule for primary immunization with the Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) is two doses given with an interval of at least 2 months A more potent Meningococcal CCRM$_{197}$ Conjugate Vaccine formulation might enable a reduction of the antigen dosage and/or a reduction in the number of doses needed in infants. One approach to achieve more potent well-characterized sub-unit vaccines - like the Meningococcal C-CRM$_{197}$ Conjugate Vaccine - is the use of new adjuvants that activate the Toll-like receptor (TLR) pathway.

GSK is developing a small molecule immune potentiator (SMIP) LHD153 that is an agonist for TLR7. The objective driving the development of LHD153 is to achieve a vaccine adjuvant with strong immunopotentiating properties and minimal side effects. In line with this objective, it has been postulated that the ideal SMIP should remain local

and target innate immune cells at the injection site. To this end, LHD153 contains a functional phosphonate group to allow for adsorption to aluminium hydroxide. The

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
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arginine salt derivative of this compound is LHD153R. Preclinical results from animal models for bacterial and viral antigens, including MenC, MenB, rabies, HIV and respiratory syncytial virus (RSV) showed increased functional antibodies and antigenspecific T-cells with LHD153R adsorbed to aluminium hydroxide (Aluminium Hydroxide/LHD153R) when compared to aluminium hydroxide adjuvanted controls. *In vitro* toxicity screens confirmed that LHD153R is not phototoxic, genotoxic or mutagenic. Furthermore, toxicology studies in dog and rats showed that intramuscular (IM) injection of Aluminium Hydroxide/LHD153R was well tolerated. Importantly, in contrast to free LHD153R, toxicokinetic analysis in rats and dogs confirmed very limited exposure of LHD153 when LHD153R was adsorbed to aluminium hydroxide after IM injection.

The aim of this Phase 1 clinical study is to assess the safety of Aluminium Hydroxide/LHD153R adjuvanted MenC-CRM_{197} conjugate vaccine (MenCCRM$_{197}$/Aluminium Hydroxide/LHD153R) and to compare the antibody-mediated immune response elicited by MenC-CRM_{197}/Aluminium Hydroxide/LHD153R with the licensed aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (Menjugate®). Furthermore, a comprehensive set of exploratory objectives has been selected to assess the systemic exposure of LHD153 after intramuscular injection of MenC-CRM_{197}/Aluminium Hydroxide/LHD153R, to evaluate the quality of the specific immune response against MenC-CRM_{197} in detail and to evaluate biomarkers that may be predictive of safety and/or innate immune activation.

The licensed Meningococcal C-CRM_{197} Conjugate Vaccine (Menjugate®) has been selected as the primary vaccine candidate to assess the safety and immunopotentiating properties of Aluminium Hydroxide/LHD153R for several reasons. Firstly, the safety and immunogenicity profiles of the Meningococcal C-CRM_{197} Conjugate Vaccine (Menjugate®) have been well established through years of commercial use. Secondly, a more potent MenC-CRM_{197} conjugate vaccine might enable a reduction of the antigen dosage or the number of doses needed in infants. Finally, MenC-CRM_{197} is a wellcharacterized, single conjugate antigen preparation which provides an ideal setting to evaluate the potential of this new Aluminium Hydroxide/LHD153R adjuvant.

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Study Objectives:

Primary Safety Objective:

To assess the safety of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R as compared to that of aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine.

Primary Immunogenicity Objective:

To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine at Day 29, as measured by human complement serum bactericidal assay (hSBA) directed against MenC.

Secondary Immunogenicity Objectives:

1. To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal CCRM$_{197}$ Conjugate Vaccine, at Day 8 and Day 181 after vaccination, as measured by hSBA directed against MenC. Baseline antibody titers will also be measured by hSBA.
2. To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal CCRM$_{197}$ Conjugate Vaccine at Day 8, Day 29 and Day 181 after vaccination, as measured by an enzyme-linked immunosorbent assay (ELISA) to MenC. Baseline antibody concentrations will also be measured by ELISA.

Exploratory Objectives:

1. To evaluate the systemic exposure of LHD153 at several early time-points after IM injection of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R or aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine.
2. To explore the frequency of B cells specific for MenC polysaccharide and CRM$_{197}$ protein at baseline (Day 1) and at Day 8, Day 29 and Day 181 after vaccination with

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MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R or the aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine. Subsequently, the B cell repertoire of the antigen specific B cells and the specific antibody functionality will be analyzed in a selected subset of subjects.

3. To explore the baseline T cell mediated immunity to CRM$_{197}$ and to evaluate the frequency and quality of CRM$_{197}$ specific T cells induced by MenC-CRM$_{197}$/Aluminium Hydroxide/ LHD153R compared to aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine at Day 8 and Day 29.
4. To evaluate biomarkers that may be predictive for safety and/or innate immune activation.

Study Design:

This Phase 1, randomized, observer-blind, dosage-escalation study will be performed at a single center. In total, approximately 80 healthy male and healthy non-pregnant female adults (18-45 years of age) will be enrolled in the study. Subjects will be randomized to receive a single IM vaccination of either the licensed aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine (i.e. 10 µg MenC conjugated to CRM$_{197}$, adjuvanted with 1 mg aluminium hydroxide) or one of four dosages of the investigational vaccine, MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R (i.e. 10 µg MenC conjugated to CRM$_{197}$, adjuvanted with 1 mg aluminium hydroxide and one of four dosages [12.5, 25, 50 or 100 µg] of LHD153R).

For the dosage-escalation of LHD153R, the subjects will be enrolled into 1 of 4 cohorts, in a stepwise manner with 20 subjects per cohort. Subjects in all cohorts will be randomized in a 1:4 ratio, to receive either aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine (control) or MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R with increasing doses of LHD153R.Cohort 1 will receive 12.5 µg of LHD153R; Cohort 2 will receive 25 µg of LHD153R; Cohort 3 will receive 50 µg of LHD 153; and Cohort 4 will receive 100 µg of LHD153R (Table 1).

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Table 1. Subjects Randomized per Cohort and Treatment Dosage Group

Cohort	Group	Subjects/ Group	MenC Dosage* (µg)	Adjuvant Dosages		Total Volume/Dose	Total Subjects/Cohort
				Aluminium Hydroxide (mg)	LHD153R (µg)		
1	A	4	10	1	0	0.5 mL	20
	B	16	10	1	12.5	0.5 mL	
2	A	4	10	1	0	0.5 mL	20
	C	16	10	1	25	0.5 mL	
3	A	4	10	1	0	0.5 mL	20
	D	16	10	1	50	0.5 mL	
4	A	4	10	1	0	0.5 mL	20
	E	16	10	1	100	0.5 mL	

*Conjugated to 12.5-25 µg CRM_{197}

After vaccination, all subjects will be confined to the clinical site for 24 hours for clinical observation, including but not limited to observations for solicited and unsolicited adverse events, body temperature measurements and blood sampling for exploratory endpoint measurements.

Importantly, all cohorts will have a staggered entry based on Data Monitoring Committee (DMC) reviews.

- For each cohort, the first 5 subjects (i.e. the first 1:4 randomization block) to receive either aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (n=1) or MenC-CRM_{197}/Aluminium Hydroxide/LHD153R (n=4) will be treated at a vaccination rate of 1 subject each day.
- After entry of the first 5 subjects in each cohort, the enrollment will be paused. The remaining 15 subjects for each cohort will be enrolled only after DMC review of the safety results obtained through Day 14 has been finalized (Table 2).
- In addition, enrollment of the first 5 subjects in the next cohort will only proceed after the Day 14 safety results of the first 5 subjects of the previous cohort have been reviewed by the DMC (Table 2).
- Furthermore, all available Day 14 and Day 29 safety results will be included in DMC reviews between the different enrollment stages.

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Table 2. Overview of staggered entry of subjects based on DMC reviews

Stage	Dosage Cohort	MenC-CRM$_{197}$/ Aluminium Hydroxide (n)	MenC-CRM$_{197}$/ Aluminium Hydroxide /LHD153R (n)
1	1	1	4
Enrollment pause until DMC review of Stage 1 Day 14 Safety Results			
2	1	3	12
	2	1	4
Enrollment pause until DMC review of Stage 1 Day 29 and Stage 2 Day 14 Safety Results			
3	2	3	12
	3	1	4
Enrollment pause until DMC review of Stage 2 Day 29 and Stage 3 Day 14 Safety Results			
4	3	3	12
	4	1	4
Enrollment pause until DMC review of Stage 3 Day 29 and Stage 4 Day 14 Safety Results			
5	4	3	12

The DMC review will be performed according to predefined stopping/pausing guidelines used to ensure the safety of study subjects. These stopping/pausing guidelines are based on FDA guidance and with grading scales from the CBER Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials". See protocol section 3.6 for further details.

Safety Measurements

Schedule of safety data collection:

- Solicited local and systemic adverse events (AEs), body temperature and all unsolicited AEs will be collected until Day 14.
- All serious adverse events (SAEs), medically attended AEs, AEs leading to study withdrawal, new onset of chronic disease (NOCDs), and adverse events of special interest (AESIs) will be collected from the date of signed informed consent to study completion at Day 366.

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- All concomitant medications administered in relation to the reported AEs will be collected from vaccination to study completion at Day 366.

Solicited local AEs include injection site erythema, injection site induration, injection site pain and injection site swelling. Solicited systemic AEs include body temperature ≥ 38.0°C (as measured orally), loss of appetite, nausea, fatigue, generalized myalgia, generalized arthralgia, headache, chills, vomiting, diarrhea, generalized rash and urticaria.

All AESIs will be reported in the same manner as SAEs. All AEs will be monitored until resolution or, if the AE becomes chronic, a cause is identified. If an AE is unresolved at the conclusion of the study, a clinical assessment will be made by the investigator and the medical monitor to determine whether or not continued follow-up of the AE is warranted.

The relationship of the study treatment to any AE will be determined by the investigator as probably related, possibly related, or not related; the relationship of the study treatment to any SAE will be determined by the investigator as probably related/suspected, or not related.

Safety Laboratory Parameters

To assess laboratory AEs, blood and urine samples will be collected from each subject as outlined in Table 3 to perform blood chemistry, hematology, and urine analyses.

Safety laboratory samples will be drawn from all subjects at pre-vaccination screening (between Day -28 and Day -3) at Day 1 (pre-vaccination and 24h after vaccination), at Day 8 and at Day 29. Safety laboratory assessments will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, liver function tests (ALT, AST), a complete blood count and C-reactive protein. A urine sample will be collected at the same time-points and will be assessed for the presence of protein, glucose and red blood cells.

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Primary and Secondary Immunogenicity Measurements

Four blood samples per subject (i.e. at Day 1, Day 8, Day 29 and Day 181) will be collected for serum preparation and determination of antibody-mediated immune responses to MenC-CRM$_{197}$ as outlined in Table 3 and Table 4. See section 7.3 for further details.

Exploratory Measurements

In all subjects who agree by signing a separate Informed Consent, additional blood samples will be collected at Day 1, Day 4, Day 8, Day 29 and Day 181 for exploratory assays as outlined in Table 3 and Table 4. The purpose of these assays is to assess the systemic exposure of LHD153, to determine the frequency and quality of B- and T-cells specific for MenC polysaccharide and/or CRM$_{197}$ and to evaluate biomarkers that may be predictive of safety and/or innate immune activation. Subsequently, MenC-CRM$_{197}$ specific B-cell repertoires as well as the MenC-CRM$_{197}$ specific antibody functionalities will be analyzed in a selected subset of subjects, dependent on the results from primary and secondary immunogenicity measurements and the volume of whole blood (specific B cell repertoire) and serum (specific antibody functionality) remaining for additional testing. See section 7.4 for further details. All exploratory analyses may be performed after the Clinical Study Report (CSR) has been completed, in which case these data will be submitted as an addendum to the CSR.

Number of Subjects planned:

Approximately 80 adult subjects will be randomized, with anticipated dropout rates of 5% by Day 181 (last serology time point), and 10%, by Day 366 (last safety time point).

Sample size is not driven by statistical assumptions for formal hypothesis testing, but the proposed number of subjects will be sufficient to provide a descriptive summary of the safety and immunogenicity of the study vaccine.

Study Population and Subject Characteristics:

Healthy adult male and female volunteers between 18-45 years of age, inclusive.

The list of inclusion and exclusion criteria is included in protocol section 4.0.

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Study Vaccines:

The MenC-CRM$_{197}$ conjugate is a lyophilized powder consisting of 10 µg of MenC polysaccharide conjugated to 12.5-25 µg CRM$_{197}$ carrier protein. The MenC-CRM$_{197}$ lyophilized powder will be reconstituted with adjuvant by the unblinded designated site staff member who is to follow the procedure as described in the vaccine preparation instructions in the Investigator Site File (i.e. the vaccine will be prepared in the clinic prior to administration).

The lyophilized MenC-CRM$_{197}$ powder will be reconstituted with either:

(a) aluminium hydroxide adjuvant

(b) Aluminium Hydroxide/LHD153R adjuvant with specified dosages of LHD153R (12.5, 25, 50 or 100 µg)

The components for each formulation of MenC-CRM$_{197}$ will be provided in a separate kit.

Aluminium Hydroxide/LHD153R with specified dosages of LHD153R will be prepared by dilution of the highest Aluminium Hydroxide/LHD153R dosage (100 µg of LHD153R) with aluminium hydroxide.

In each cohort, subjects will be randomized to receive one injection of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R adjuvant or aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine. The 0.5 mL of vaccine will be injected IM in the deltoid muscle, with preference that the injection is administered in the nondominant arm.

Primary Safety Endpoint:
Safety will be assessed by measuring the frequency of local and systemic solicited AEs, unsolicited AEs, SAEs, AESIs, NOCDs, and safety laboratory data for all subjects. Specifically,

- The frequency and percentage of subjects with solicited local and systemic AEs through Day 14. Time intervals after vaccination that will be summarized are: 30 min post-vaccination, Days 1-4 (without 30 min), Days 5-8, Days 8-14, Days 1-8

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
GlaxoSmithKline Biologicals S.A.	V132_01EXP	MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and Meningococcal C-CRM$_{197}$ Conjugate Vaccine

(without 30 min) and Days 1-14 (without 30 min).

- The frequency and percentage of subjects with any unsolicited AEs from the day of vaccination (Day 1) to Day 14.
- The frequency and percentage of subjects with SAEs, medically attended AEs, AEs leading to study withdrawal, NOCDs, AESIs for the following time periods: day of signed informed consent until study completion (Day 366), day of vaccination (Day 1) to Day 29 and Day 29 to study completion (Day 366).
- The absolute values and changes in hematology, chemistry, and urinalysis parameters.
- The frequency and percentage of subjects with abnormal laboratory parameter values as classified by investigator normal ranges (low, normal, high) and as classified by CBER toxicity grading scales, when available.

Primary Immunogenicity Endpoint:

Geometric mean titers (GMTs) measured by hSBA directed against MenC from samples collected on Day 1 (baseline, before vaccination) and Day 29 as well as the GMR of the titers (Day 29 / Day 1).

Secondary Immunogenicity Endpoints:

- GMTs and corresponding GMRs measured by hSBA directed against MenC for samples collected at Day 8 and Day181.
- Percentage of subjects with hSBA seroresponse at Day 8, Day 29, and Day 181. seroresponse is defined as a post vaccination hSBA ≥8 for subjects with a baseline hSBA <4 or have an increase of at least 4 times the baseline hSBA level for subjects with pre-vaccination hSBA ≥4.
- Antibody geometric mean concentrations (GMCs) against MenC measured by ELISA for samples collected on Day 1 (baseline, prior to vaccination), Day 8, Day 29, and Day 181.
- The percentage of subjects with at least a 4-fold increase in antibody concentrations to MenC measured by ELISA on Day 8, Day 29, and Day 181 relative to baseline

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
GlaxoSmithKline Biologicals S.A.	V132_01EXP	MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and Meningococcal C-CRM$_{197}$ Conjugate Vaccine

(Day 1).

Exploratory Endpoints:

Testing and analyses of exploratory endpoints may be performed after the Clinical Study Report (CSR) has been completed, in which case these data will be submitted as an addendum to the CSR.

1. Serum concentration of LHD153 at Day 1 baseline (prior to vaccination), Day 1 (1h , 2h, 4h, 8h, and 24h after vaccination) and Day 4 by LC-MS/MS.
2. Frequency of MenC polysaccharide-specific and CRM$_{197}$-specific B cells at Day 1 (baseline), Day 8, Day 29, and Day 181 by ELISPOT.
3. Diversity of the MenC polysaccharide-specific B-cell repertoire at Day 1 (baseline), Day 8, Day 29, and Day 181 by immunoglobulin cDNA sequencing.
4. Functionality of antigen specific antibodies will be assessed at Day 1 (baseline), Day 8, Day 29, and Day 181 by analysis of immunoglobulin isotype, glycosylation state and their ability to fix complement, to promote antibody-dependent cell mediated cytoxicity, to induce phagocytosis and to activate FcR+ cells. If the quantity of serum available for this specific exploratory objective is limited, assessments of immunoglobulin isotype and glycosylation state will be prioritized over the other assessments.
5. Frequency and quality of T cells specific for CRM$_{197}$ at Day 1 (baseline), Day 8, and Day 29 by flow cytometry using intracellular staining with a panel of cytokines and staining of surface markers to identify cell populations.
6. Serum concentrations of a panel of 30 chemokines and cytokines at Day 1 baseline (prior to vaccination), Day 1 (6h and 24h after vaccination), Day 4, and Day 8 by electrochemo-luminescence based assay.
7. Gene expression profile in whole blood at Day 1 baseline (prior to vaccination), Day 1 (6h and 24h after vaccination), Day 4, and Day 8 by RNA micro array analysis.

8. Number and activation status of myeloid and lymphoid cell populations at Day 1 baseline (prior to vaccination), Day 1 (24h after vaccination), Day 4 and Day 8 by

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
GlaxoSmithKline Biologicals S.A.	V132_01EXP	MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and Meningococcal C-CRM$_{197}$ Conjugate Vaccine

flow cytometry.

Statistical Analyses:

The study is exploratory in nature, thus analyses will be descriptive and no formal hypothesis testing will be performed.

Primary Safety Analyses

The primary safety analyses will be based on the safety set for solicited and unsolicited adverse events. There is no statistical null hypothesis associated with the safety objective, which will be analyzed descriptively.

Immunogenicity Analyses

The primary immunogenicity analyses will be based on the per-protocol set (PPS) on Day 29. The primary analyses will also be performed using the Full Analysis Set (FAS) as a measure of the sensitivity/robustness of the results. All other immunogenicity assessments will be performed using the PPS or the appropriate subset of subjects. The antibody concentrations/titers will be summarized using GMC/GMTs and two-sided 95% confidence intervals (CIs) constructed by exponentiation (base 10) of the least square means of the logarithmically transformed (base 10) antibody titer. The 95% CIs will be obtained from an analysis of covariance (ANCOVA) with baseline concentration/titer as a covariate. Additional details will be further described in the Statistical Analysis Plan.

The immunogenicity endpoints based on subjects meeting criteria for seroconversion or achieving a certain threshold value will be summarized using frequencies and percentages and associated two-sided 95% Clopper-Pearson CIs. For analyses of seroconversion, separate summaries may be provided based on seropositivity status at baseline.

Interim Analysis: An Interim Analysis will be performed on the immunogenicity and safety data collected from all subjects until Day 29, after all cohorts have been enrolled. Further details

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
GlaxoSmithKline Biologicals S.A.	V132_01EXP	MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and Meningococcal C-CRM$_{197}$ Conjugate Vaccine
regarding the interim analysis are contained in section 8.6.		
Data Monitoring Committee: A DMC will be implemented to review safety data during scheduled periodic reviews. The DMC will review safety data collected until Day 14, as described in the DMC charter and in the Statistical Analysis Plan, after enrollment of the first 5 subjects in each cohort, before proceeding with enrollment of the remaining 15 subjects in each cohort. In addition, enrollment of the first 5 subjects of the next cohort will only proceed after the Day 14 safety results of the first 5 subjects of the previous cohort have been reviewed. Furthermore, all available Day 14 and Day 29 safety results will be included in DMC reviews between the different enrollment stages. Further information regarding the DMC is discussed in more detail in the protocol, section 3.7.		

Table 3: Time and Events Table – Treatment Period (until Day 29)

	Visit Type	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit	Phone Call	Clinic Visit
	Study Day	**-28 to -3**	**1**	**4**	**8**	**15**	**22**	**29**
	Visit Window (Days)	**n/a**	**n/a**	**n/a**	**-1/+1**	**+1**	**n/a**	**-2/+2**
	Visit Number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**
Study Event	**References**							
Study Treatment								
Vaccination	Section 5.2		X					
Screening and Safety								
Informed Consent	Section 5.1.1	X						
Demographic Data & Medical History	Sections 5.1.2	X						
Physical Exam	Sections 5.1.2 and 5.2.1	X	X[a]					
Safety Laboratory blood draw (10 ml)	Section 7.1.7	X	X[b]		X			X
Urinalysis	Sections 7.1.7	X	X[b]		X			X
Pregnancy Test	Sections 5.1.2 and 5.2.1	X	X[a]					
Exclusion/Inclusion Criteria	Section 4.0	X	X[a]					
Randomization	Section 5.2.3		X[a]					
30 min and 24 hr Post Injection Assessment	Section 5.2.5		X[c]					
Subject Diary Dispensed with Training	Section 5.2.5		X					
Subject Diary Reminder	Section 5.2.5			X	X			

Subject Diary Reviewed and Collected	Section 5.3.1					X		
Assess all solicited AEs	Section 7.1.1 and 7.1.3					X		
Assess all unsolicited AEs	Sections 7.1.2 and 7.1.3	X	X	X	X	X		

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	Visit Type	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Phone Call**	**Clinic Visit**
	Study Day	**-28 to -3**	**1**	**4**	**8**	**15**	**22**	**29**
	Visit Window (Days)	**n/a**	**n/a**	**n/a**	**-1/+1**	**+1**	**n/a**	**-2/+2**
	Visit Number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**
Study Event	**References**							
Assess SAEs	Section 7.1.4	X	X	X	X	X	X	X
Assess AESIs	Section 7.1.4.1	X	X	X	X	X	X	X
Assess NOCDs, medically attended AEs, AEs leading to withdrawal	Sections 7.1.3	X	X	X	X	X	X	X
Assess relevant medications	Sections 5.1.2 and 6.5	X	X	X	X	X	X	X
Blood draws for Immunogenicity and Exploratory Objectives								
Serum Blood Draws (Primary/Secondary Objectives; 10 mL)	Section 3.5		X_a		X			X
Serum Blood Draws (Exploratory Objectives; 5 mL)	Section 3.5		X_d	X	X			
Whole Blood Draws (Exploratory Objectives; 3 mL)	Section 3.5		X_e	X				
Whole Blood Draws (Exploratory Objectives; 5 mL)	Section 3.5		X_f	X	X			
Whole Blood Draws (Exploratory Objectives; 20 mL)	Section 3.5		X_g	X				
Whole Blood Draws (Exploratory Objectives; 50 mL)	Section 3.5							X

Whole Blood Draws (Exploratory Objectives; 70 mL)	Section 3.5		Xa		X			

Notes: ɔn.

a. Procedure must be performed prior to vaccination.
b. Two blood draws (2 x 10 ml) and two urine samples must be taken at Study Day 1, i.e. at baseline (prior to vaccination) and at 24h after vaccinati
c. Body temperature measurement must be performed at 30 min, 2, 4, 6, 8, 10, 12, 18 and 24h after vaccination.
d. Three Serum Blood Draws (3 x 5ml) must be taken at Study Day 1, i.e. at baseline (prior to vaccination), at 6h and at 24h after vaccination.
e. Six Whole Blood Draws (6 x 3 mL) must be taken at Study Day 1, i.e. at baseline (prior to vaccination) and at 1, 2, 4, 8 and 24h after vaccination.
f. Three Whole Blood Draws (3 x 5 mL) must be taken at Study Day 1, i.e. at baseline (prior to vaccination), at 6h and at 24h after vaccination.
g. Whole Blood Draw (20 mL) at Study Day 1 must be taken at 24h after vaccination.

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Table 4: Time and Events Table – Follow-up Period (until Day 366)

	Visit Type	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Phone Call**	**Phone Call**	**Clinic Visit**
	Study Day	**85**	**113**	**181**	**209**	**271**	**366**
	Visit Window (Days)	**-7 to +7**	**-7 to +7**	**-7 to +7**	**-14 to +14**	**-14 to +14**	**-14 to +14**
	Visit Number	**7**	**8**	**9**	**10**	**11**	**12**
Study Event	**References**						
Safety							
Assess SAEs	Section 7.1.4	X	X	X	X	X	X
Assess AESI	Section 7.1.4.1	X	X	X	X	X	X
Assess NOCDs, medically attended AEs, AEs leading to withdrawal	Sections 7.1.3	X	X	X	X	X	X
Assess relevant medications	Sections 5.1.2 and 6.5	X	X	X	X	X	X
Blood draws for Immunogenicity and Exploratory Objectives							

Serum Blood Draw (Secondary Objective; 10 mL)	Section 3.5			X			
Whole Blood Draw (Exploratory Objectives; 50 mL)	Section 3.5			X			
Study Completion Procedures							
Study Termination[a]	Section 5.5						X

Notes:
a. Subjects who terminate the study early are recommended to complete certain study-related procedures. See section 5.5 for further details.

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LIST OF ABBREVIATIONS

ADCC	Antibody-dependent cell mediated cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BZN	Benzonaphthyridines
CBER	Center for Biologics Evaluation and Research
cDNA	Complementary deoxyribonucleic acid
CI	Confidence interval
CRF	Case report form
CRM_{197}	Cross Reacting Material 197
CSR	Clinical Study Report
DMC	Data Monitoring Committee
EC	Ethics committee
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
ELISPOT	Enzyme-Linked ImmunoSpot
EMA	European Medicines Agency
FACS	Fluorescence-activated cell sorting
FAS	Full analysis set
FDA	Federal Drug Agency
GCP	Good clinical practice
GMC	Geometric mean concentration
GMP	Good manufacturing practice

GMT	Geometric mean titer
GMR	Geometric mean ratio
HEENT	Head, ears, eyes, nose and throat
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
hSBA	Human complement serum bactericidal assay
ICF	Informed consent form
ICH	International Committee for Harmonization
IM	Intramuscular
IRB	Institutional review board
IV	Intravenous
LLQ	Lower limit of quantification
MenC	Meningococcal type C
MPL	Monophosphoryl lipid A
NCR	No carbon required
NOCD	New Onset of Chronic Disease
PEG	Polyethylene glycol
PO	Per oral
PP	Per protocol
RNA	Ribonucleic acid (RNA
SAE	Serious Adverse Event
SMIP	Small molecule immune potentiator
TLR	Toll-like receptor
VSAE	Vaccine serious adverse event

1.0 BACKGROUND AND RATIONALE

1.1 Background

MenC-CRM$_{197}$ Conjugate Vaccine

Meningococcal disease worldwide is predominantly a disease of infants and young children. *N. meningitidis* serogroup B and C remain the most prevalent strains in North America and Europe, (Rosenstein, N. et al., 2001) and together cause more than 95% of reported cases of meningococcal disease in Europe (Connolly, M, et al., 1999). In Europe, *N. meningitidis* serogroup C (MenC) is one of the major serogroups causing invasive disease. Case fatality in Germany has ranged between 6% and 8% between 1999 and 2006, and has remained generally consistent across the different European countries, varying between 6-11%, with the case fatality rate being notably higher for serogroup C disease than for serogroup B (European Centre for Disease Prevention and Control, 2011). Since MenC vaccination was added to Germany's routine schedule for children in 2006, there has been a reported decline in MenC incidence. However, the decline was not as rapid when compared to other European countries (Hellenbrand, W. et al., 2013).

The GSK Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) comprises MenC oligosaccharides conjugated to the protein carrier, CRM$_{197}$, a nontoxic mutant of diphtheria toxin. The vaccine has been shown to be safe and immunogenic and able to prime infants, toddlers and young children for immunological memory (see Meningococcal C-CRM$_{197}$ Conjugate Vaccine Summary of Product Characteristics).

In Germany, the Standing Committee on Vaccination (STIKO) of the Robert Koch Institute recommends a single dose of MenC conjugate vaccine in children over the age of 12 months as part of the routine vaccination campaign (Robert Koch Institute Epidemiologisches Bulletin, August 2013). For specific indications, e.g. in case of postexposure prophylaxis, the recommended schedule for primary immunization of infants between 2 to 12 months of age with a MenC conjugate vaccine is two dosages given with an interval of at least 2 months.

Although the Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) represents an example of how vaccination with a well characterized, purified polysaccharide antigen can yield pivotal public health triumphs, there remains a need for further improvement of the MenC vaccine. A more potent MenC vaccine formulation might yield an increase in the magnitude of the antigen-specific immune response enabling a reduction of the antigen dosage. Furthermore, induction of a more rapid antigen-specific immune response may enable a reduction in the number of doses needed for post-exposure prophylaxis in infants.

Vaccine Adjuvants

Immunization with purified protein or polysaccharide antigens typically results in the induction of a modest antibody response with little or no T cell response when compared to vaccines comprised of whole or killed bacteria or viruses that have inherent immunepotentiating activity. The need to increase the immunogenic response of wellcharacterized and purified antigens that display suboptimal immunogenicity when used alone affirms the essential role for the use of adjuvants. Vaccine adjuvants may significantly reduce the amount of antigen needed (Del Giudice, G, et al., 2013) and may induce a more rapid immune response enabling a reduction in the number of doses in a regimen.

Besides reducing the antigen dosage or number of doses in the vaccine regimen, there is now an increased appreciation of the capacity of adjuvants to increase not just overall antibody titer but also to increase the number of functional antibodies and/or antibodies with higher affinity for vaccine antigens. Many pathogens, such as influenza viruses, HIV, human papilloma virus (HPV) and the malaria parasite, display substantial antigenic drift, subtype and/or strain variations. Therefore, the ability of adjuvants to broaden an immune response profile could be crucial to the success of vaccines against such targets. Previous studies have shown that the broadening effect of adjuvants may be mediated via expansion of B cell diversity, not merely through increased titers (Khurana, et al., 2010, 2011). Clinically, antibody response broadening by adjuvants such as AS04 or oil-inwater emulsions has been demonstrated in HPV vaccines and influenza, respectively (Bissett, SL et al., 2014; Del Giudice, G et al., 2013).

One unmet need is the development of vaccines for effective T cell responses. Several vaccines in development are aimed at eliciting T cell responses, which historically have not been induced by the most commonly used adjuvants in vaccines for human use, such as aluminium hydroxide. Therefore, an objective of many adjuvant discovery and development programs is to elicit more effective engagement of T-helper cells for optimizing the quality, breadth and durability of antibody responses, or, to induce effector CD4+ or CD8+ T cells to kill intracellular pathogens. One approach for new generation vaccines is the use of agonists for Toll-like receptors (TLRs) that activate innate immune receptors, mainly on antigen presenting cells, and facilitate the generation of T helper cell responses.

Adjuvants that are currently employed in human vaccines licensed for use in the USA and/or Europe include aluminium salts, oil-in-water emulsions (MF59, AS03 and AF03), virosomes, and AS04 (Alving, CR, et al., 2012). Among the most advanced adjuvants systems is AS04 which is used in the Cervarix® HPV vaccine and consist of the TLR4 ligand monophosphoryl lipid A (MPL) combined with aluminium salt. MPL, along with

QS21, is also part of the adjuvant system (AS01) in the RTS, S malaria vaccine which has been evaluated in a Phase 3 clinical trial (Regules, JA, et al., 2011). Another clinically advanced adjuvant is CpG oligodeoxynucleotide (ODN), a TLR9 ligand contained in the Heplisav® vaccine candidate for hepatitis B from Dynavax, that has completed a Phase 3 clinical trial (Reed, SG, et al., 2013).

Small molecule immune potentiators as a new class of vaccine adjuvants

A new class of adjuvants, small molecule immune potentiators (SMIPs), has been identified that activate immune cells by targeting TLR7 and TLR8. Imiquimod and Resiquimod (R848) are clinically advanced TLR7 and/or TLR8 SMIPs that are used as immunotherapeutics. Although Imiquimod and Resiquimod have been studied extensively as vaccine adjuvants in preclinical models (Vasilakos et al. 2013), they were never optimized for this use and, in general, compare poorly to other pre-clinical and clinical adjuvant candidates. Furthermore, when Imiquimod is applied topically (it is a licensed topical treatment for viral and malignant skin lesions) it induces strong local and systemic inflammatory reactions, and is poorly tolerated (Bauza, et al. 2009; Campanelli, et al. 2005; Meyer, et al. 2008).

Unlike traditional drugs, TLR7 SMIPs activate innate immunity and initiate a cascade of immune responses that can have systemic impact and endure after the compound has been cleared from the organism. For SMIPs as vaccine adjuvants this difference is highlighted further by the fact that 2-3 local IM injections drive antigen-specific B and T cell responses at distal sites and these can provide protection in the form of immunologic memory (Tacken, et al. 2011; Ilyinskii, et al., 2014). Therefore, limiting the systemic exposure of the SMIP adjuvants has been postulated as an approach to both increase vaccine efficacy and minimize side effects associated with systemic and generalized inflammation. GSK is currently developing a novel adjuvant, containing a SMIP from the benzonaphthryridines (BZN) series, LHD153, which targets TLR7. The objective driving the discovery of this new TLR7 ligand was to develop a vaccine adjuvant with high efficacy in increasing the vaccine specific immune response and with minimal side effects. To obtain this objective it was postulated that the ideal compound would remain localized at the site of injection to help trigger the immune reaction to vaccine antigens, yet maintain a low systemic distribution. At the same time this compound had to be soluble to make industrial scale-up and manufacturing feasible. Soluble BZN were engineered so that they could be formulated with aluminium salts with the aim of limiting their systemic exposure and keeping them localized in the muscle for short time after immunization. The strongest adsorption to aluminium hydroxide particles is obtained through ligand exchange of hydroxyl and/or phosphate groups on the surface of aluminium hydroxide or phosphate with soft anionic moieties such as phosphates, phosphonates, phosphites, sulfates and carboxylates. To drive the adsorption to

aluminium hydroxide through ligand exchange, LHD153 was functionalized with a polyethylene glycol (PEG) linker and a terminal phosphonate. Furthermore, LHD153 was stabilized with arginine salt to allow scale up for GMP manufacturing, yielding LHD153R. As predicted, unformulated LHD153R exhibited high levels of systemic exposure when injected IM in mice, rats and dogs, whereas the serum concentrations of LHD153R adsorbed to aluminium hydroxide (Aluminium Hydroxide/LHD153R) was dramatically reduced. Moreover, Aluminium Hydroxide/LHD153R remained localized to the injection site.

Preclinical studies using Aluminium Hydroxide/LHD153R to date confirm the activation of the TLR7 pathway and subsequent boost of both the humoral and cellular immune response. Moreover, Aluminium Hydroxide/LHD153R displays a unique pharmacokinetic profile as demonstrated by its minimal systemic exposure, potentially minimizing any systemic inflammatory response associated with tolerability issues. Aluminium hydroxide/LHD153R has achieved proof of concept in animal models using several vaccine antigens including MenC, MenB, rabies, HIV and respiratory syncytial virus (RSV). In vitro toxicity of LDH153R has been assessed, and in vivo nonclinical tolerability and safety of LHD153R and Aluminium Hydroxide/LHD153R have been evaluated in rats, dogs and non-human primates. LHD153R was not phototoxic, genotoxic or mutagenic (Ames and chromosomal aberration tests), and did not cause local or systemic toxicity in dogs or rats. Furthermore, Aluminium Hydroxide/LHD153R was well tolerated in rhesus monkeys.

1.2 Rationale

The aim of this study is to assess the safety of Aluminium Hydroxide/LHD153R adjuvanted MenC-CRM$_{197}$ conjugate vaccine (MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R) and to compare the antibody-mediated immune response elicited by MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R with the licensed aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®).

Furthermore, a comprehensive set of exploratory objectives has been selected to assess the systemic exposure of LHD153 after intramuscular injection and to evaluate the quality of the specific immune response against MenC-CRM$_{197}$ in detail and to evaluate biomarkers that may be predictive of safety and/or innate immune activation.

The licensed Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) has been chosen as the primary vaccine candidate to assess the safety and immunopotentiating properties of Aluminium Hydroxide/LHD153R for several reasons. Firstly, the safety and immunogenicity profiles of the Meningococcal C-CRM$_{197}$ Conjugate Vaccine have been well established through years of commercial use. Secondly, a more potent

Meningococcal C-CRM$_{197}$ Conjugate Vaccine might enable a reduction of the antigen dosage or the number of doses needed in infants between 2 and 12 months of age. Finally, Meningococcal C-CRM$_{197}$ is a well-characterized, single conjugate antigen preparation which provides an ideal setting to explore the potential of this new Aluminium Hydroxide/LHD153R adjuvant.

2.0 OBJECTIVES

2.1 Primary Objectives

Primary Safety Objective

To assess the safety of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R as compared to that of aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine.

Primary Immunogenicity Objective

To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine at Day 29, as measured by human complement serum bactericidal assay (hSBA) directed against MenC.

2.2 Secondary Objectives

Secondary Immunogenicity Objective(s)

1. To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal CCRM$_{197}$ Conjugate Vaccine at Day 8 and Day 181 after vaccination, as measured by hSBA directed against MenC. Baseline antibody titers will also be measured by hSBA.
2. To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal CCRM$_{197}$ Conjugate Vaccine, at Day 8, Day 29 and Day 181 after vaccination, as measured by an enzyme-linked immunosorbent assay (ELISA) to MenC. Baseline antibody concentrations will also be measured by ELISA.

2.3 Exploratory Objectives

1. To evaluate the systemic exposure of LHD153 at several early time-points after IM injection of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R or Meningococcal CCRM$_{197}$ Conjugate Vaccine.
2. To explore the frequency of B cells specific for MenC polysaccharide and CRM$_{197}$ protein at baseline (Day 1) and at Day 8, Day 29 and Day 181 after vaccination with MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R or the aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine. Subsequently, the B cell repertoire of the antigen specific B cells and the specific antibody functionality will be analyzed in a selected subset of subjects.
3. To explore the baseline T cell mediated immunity to CRM$_{197}$ and to evaluate the frequency and quality of CRM$_{197}$ specific T cells induced by MenCCRM$_{197}$/Aluminium Hydroxide/ LHD153R compared to aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine at Day 8 and Day 29.
4. To evaluate biomarkers that may be predictive for safety and/or innate immune activation.

3.0 STUDY DESIGN

3.1 Overview of Study Design

This is a Phase 1, randomized, observer blind, adjuvant dosage-escalation study. It will be performed at a single center. In total, approximately 80 healthy male and healthy nonpregnant female adults (18-45 years of age) will be enrolled in the study.

Subjects will be randomized to receive a single IM vaccination of either the licensed aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (Menjugate®) or the investigational vaccine, MenC-CRM_{197}/Aluminium Hydroxide/LHD153R.

The dosage of LHD153R will be escalated from 12.5 µg to 100 µg. For the dosageescalation of LHD153R, the subjects will be enrolled into 1 of 4 cohorts, in a stepwise manner with 20 subjects per cohort. Subjects in all cohorts will be randomized in a 1:4 ratio, to receive either aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (control) or MenC-CRM_{197}/Aluminium Hydroxide/LHD153R with increasing doses of LHD153R. Subjects assigned to MenC-CRM_{197}/Aluminium Hydroxide/LHD153R in Cohort 1 will receive 12.5 µg of LHD153R; Subjects in Cohort 2 will receive 25 µg of LHD153R; Subjects in Cohort 3 will receive 50 µg of LHD153R; Subjects in Cohort 4 will receive 100 µg of LHD153R (Table 3.1-1).

Table 3.1-1: Subjects Randomized per Cohort and Treatment Dosage Group

Cohort	Group	Subjects/ Group	MenC Dosage* (µg)	Adjuvant Dosages		Total Volume/Dose	Total Subjects/Cohort
				Aluminium Hydroxide (mg)	LHD153R (µg)		
1	A	4	10	1	0	0.5 mL	20
	B	16	10	1	12.5	0.5 mL	
2	A	4	10	1	0	0.5 mL	20
	C	16	10	1	25	0.5 mL	
3	A	4	10	1	0	0.5 mL	20
	D	16	10	1	50	0.5 mL	
4	A	4	10	1	0	0.5 mL	20
	E	16	10	1	100	0.5 mL	

*Conjugated to 12.5-25 µg CRM_{197}

All cohorts will have a staggered entry. For each cohort, the first 5 subjects (i.e. the first 1:4 randomization block) to receive either aluminium hydroxide adjuvanted

Meningococcal C-CRM$_{197}$ Conjugate Vaccine (n=1) or MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R (n=4) will be vaccinated at rate of 1 subject each day.

After entry of the first 5 subjects in each cohort, the enrollment will be paused. The remaining 15 subjects for each cohort will be enrolled only after DMC review of the safety results obtained through Day 14 has been finalized (Table 3.1-2). In addition, enrollment of the first 5 subjects of the next cohort will only proceed after the Day 14 safety results of the first 5 subjects of the previous cohort have been reviewed by the DMC. Furthermore, all available Day 14 and Day 29 safety results will be included in DMC review between the different enrollment stages.

Table 3.1-2: Overview of staggered entry of subjects based on DMC reviews

Stage	Dosage Cohort	MenC-CRM$_{197}$/ Aluminium Hydroxide (n)	MenC-CRM$_{197}$/ Aluminium Hydroxide /LHD153R (n)
1	1	1	4
Enrollment pause until DMC review of Stage 1 Day 14 Safety Results			
2	1	3	12
	2	1	4
Enrollment pause until DMC review of Stage 1 Day 29 and Stage 2 Day 14 Safety Results			
3	2	3	12
	3	1	4
Enrollment pause until DMC review of Stage 2 Day 29 and Stage 3 Day 14 Safety Results			
4	3	3	12
	4	1	4
Enrollment pause until DMC review of Stage 3 Day 29 and Stage 4 Day 14 Safety Results			
5	4	3	12

Post-vaccination procedures include collection of urine specimens at Day 1, Day 8 and Day 29 for safety assessment and blood specimens at Day 1, Day 8, Day 29 and Day 181 for safety assessment and evaluation of the primary and secondary immunogenicity endpoints. Furthermore, additional blood specimens will be collected for assessment of exploratory endpoints at Day 1, Day 4, Day 8, Day 29 and Day 181 from those subjects that signed an additional informed consent concerning blood collection for exploratory assessment.

3.2 Study Period

Each subject should expect to participate in the study for approximately 12 months, from the time of enrolment through the last study visit.

3.3 Blinding Procedures

This study is designed as an observer-blind study. For each dosage cohort, subjects, investigators, laboratories and the sponsor will be blinded to vaccine assignments.

To maintain the blindness within each cohort, designated nurse(s) or physician(s) will be responsible for administering the study vaccines to the subjects, and will be instructed not to reveal the identity of the study vaccines neither to the subject nor to the investigative site personnel (investigator, study nurse, monitor) involved in the conduct or monitoring of the trial. This (these) designated individual(s) will have no contact with the subjects after the administration of the study vaccine. Furthermore, unblinded monitors are assigned to reconcile actual vaccine treatment.

Study unblinding, at the group level, is planned for an Interim Analysis of the safety and immunogenicity data obtained up to Day 29 after all cohorts are enrolled and for full unblinding at the End of Study.

Except in the case of medical necessity, a subject's treatment should not be unblinded without the approval of the Sponsor. In such instance of medical emergency, every effort should be made to contact the Sponsor prior to unblinding. If unblinding should occur (by either accidental unblinding or emergency unblinding for a serious adverse event) prior to completion of the study, the investigator must promptly contact the Sponsor and document the circumstances on the appropriate forms. Instructions regarding emergency unblinding will be provided to the investigator.

3.4 Data Collection

3.4.1 Data Collected from Subjects

The following data will be collected from each subject over the duration of their study participation:

- Demographic Information
- Adverse Events
- Medical History
- Concomitant Medications
- Vital signs

All data collected must only be identified using the Subject ID, as described in section 5.2.3.

3.4.2 Tools Used for Data Collection

Data will be recorded in the Subject Diary and collected on Case Report Forms (CRFs).

Subject Diary

Subject Diaries will be the only source document allowed for solicited local and systemic adverse events (including body temperature measurements), starting after the initial 24 hours post-vaccination observation period at the clinic. The following additional rules apply to documentation of safety information collected in the Subject Diary:

1. No corrections or additions to the Subject Diary will be allowed after it is delivered to the site.
2. Any blank or illegible fields on the Subject Diary must be described as missing in the CRF.
3. Any corrections to the Subject Diary must be performed by the person completing the Subject Diary and should include a single strike through line through the incorrect value or text with a brief explanation for each change, the initials of that person, and date of correction.

Case Report Forms

This study utilizes CRFs to collect study-related data from each subject. A qualified site staff member(s) is required to enter subject data in the CRFs based on the medical information available in each subject's record. The following additional rules apply to documentation of Subject Diary information collected in the CRFs:

1. The site must enter all readable entries in the Subject Diary into the CRF, including those values that may be biologically implausible (e.g. body temperature: 400°C).
2. Any illegible or implausible data should be reviewed with the subject. If an underlying solicited or unsolicited adverse event is described on review with the subject, this should be described in the source document and reported as an unsolicited adverse event in the appropriate CRF (e.g., if the subject above confirms body temperature of 40°C on the day in which body temperature: 400°C was written into his/her Subject Diary, this fever of 40°C should be recorded in the appropriate CRF).

3. Any newly described safety information (including a solicited adverse event) must not be written into the Subject Diary and must be described in the study file as a verbally reported adverse event. Any adverse event reported in this fashion must be described as an unsolicited adverse event and therefore, entered in the appropriate CRF.

Data should be entered into the CRF in a timely fashion following each subject's clinic visit, study procedure, or phone call. Each subject's CRF casebook will be compared with the subject's source records by a GSK-approved study monitor (or designee) over the duration of the study in order to ensure data collection accuracy.

3.5 Collection of Clinical Specimens

The following clinical specimens are required to be collected from each subject in this study:

- Blood
- Urine

Processing of each specimen should be completed by a qualified site member. Testing of clinical specimens will be performed by a GSK or designated laboratory.

Blood Specimens

Before Vaccination

- At the Pre-vaccination Screening Visit (between Day -28 to -3) one sample of approximately 10 ml blood will be drawn from all subjects.
- At Visit 1 (Day 1) - prior to vaccination – two samples of approximately 10 ml blood will be drawn from all subjects.
- At Visit 1 (Day 1) - prior to vaccination - the following blood samples will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays:
  - One sample of approximately 3 ml
  - Two samples of approximately 5 ml
  - One sample of approximately 70 ml

After Vaccination

- At Visit 1 (Day 1) - 1 hour after vaccination - one sample of approximately 3 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 2 hours after vaccination - one sample of approximately 3 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 4 hours after vaccination - one sample of approximately 3 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 6 hours after vaccination – two samples of approximately 5 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 8 hours after vaccination - one sample of approximately 3 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 24 hours after vaccination - one sample of approximately 10 ml blood will be drawn from all subjects.
- At Visit 1 (Day 1) - 24 hours after vaccination - the following blood samples will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays:
  - One sample of approximately 3 ml
  - Two samples of approximately 5 ml
  - One sample of approximately 20 ml
- At Visit 2 (Day 4) the following blood samples will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays:
  - One sample of approximately 3 ml
  - Two samples of approximately 5 ml
  - One sample of approximately 20 ml
- At Visit 3 (Day 8) two samples of approximately 10 ml blood will be drawn from all subjects.

- At Visit 3 (Day 8) the following blood samples will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays
  - Two samples of approximately 5 ml
  - One sample of approximately 70 ml
- At Visit 6 (Day 29) two samples of approximately 10 ml blood will be drawn from all subjects.
- At Visit 6 (Day 29) one sample of approximately 50 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 9 (Day 181) one sample of approximately 10 ml blood will be drawn from all subjects.
- At Visit 9 (Day 181) one sample of approximately 50 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.

The blood will be used for screening and safety laboratory assessments, immunological serology assays, pharmacokinetic analysis, cell mediated immunity assays and gene expression and protein production assays. See section 5.1.2, section 5.2.1 and section 7.0 for additional details.

Processing of each blood specimen should be completed in accordance with the study specific Clinical Specimen Laboratory Manual.

The total amount of blood collected over the study period for all subjects will be approximately 90 ml.

For subjects that signed an additional informed consent for blood collection for exploratory assays the total amount of blood collected over the study period will be approximately 441 ml.

Urine Specimens

Urine will be collected at the Pre-vaccination Screening Visit (between Day -28- to -3), at Visit 1 (Day 1; before vaccination and 24 hours after vaccination), at Visit 3 (Day 8) and at Visit 6 (Day 29). Results will be recorded in the source document and CRF.

Urine will be collected from all subjects for safety laboratory assessments and drugs-ofabuse testing. Furthermore, urine will be collected for pregnancy testing in all females.

3.6 Stopping/Pausing Guidelines

Stopping/pausing guidelines are predefined criteria that halt the conduct of a study (either a vaccine group or the entire study). These guidelines are used to ensure the safety of study subjects.

The following criteria, based on FDA guidance and with grading scales adapted from the CBER Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive vaccine Clinical Trials", will be used for this study:

1. The study will be halted (no new enrollments and no further investigational product administered until a full safety review by the DMC and consultation with the IRB/EC and the health authorities is completed) if one of the following occurs
   a. One subject experiences a serious adverse event (SAE) assessed as possibly or probably related to investigational product or,
   b. There is a subject death assessed as possibly or probably related to the investigational product.
2. If one or more subjects experience a Grade 4 AE (see Appendix C, D, and E), vital sign or clinically significant laboratory abnormality that cannot be clearly attributed to another cause, vaccination will be suspended until a full safety review by the DMC is performed.
3. If six or more subjects experience a Grade 3 AE (see Appendix A, B, C, D, and E), vital sign or clinically significant laboratory abnormality, dosage escalation will be suspended for that vaccine until a full safety review by the DMC is performed.

The sponsor or the investigator (following consultation with the sponsor) has the right to discontinue the study at any time. If the clinical study is prematurely terminated, the investigator must promptly inform the study subjects and must assure appropriate therapy and follow-up for the subjects. All procedures and requirements pertaining to the archiving of the documents must be followed. All other study materials (such as study vaccines) must be returned to the sponsor or destroyed after sponsor approval.

3.7 Data Monitoring Committee

A DMC will be formed to review safety data during scheduled periodic reviews. The DMC may also perform reviews on an ad hoc basis as needed. DMC membership will

consist of at least 3 individuals who are external to the site and sponsor, and will include 1 statistician who is independent from the study team.

Subjects will be enrolled in a stepwise manner in each of the four vaccine dosage cohorts (Cohort 1: 12.5 µg LHD153R, Cohort 2: 25 µg of LHD153R, Cohort 3: 50 µg of LHD153R and Cohort 4: 100 µg of LHD153R). The DMC will review all safety data, as described in the DMC charter and in the Statistical Analysis Plan, after the first 5 subjects in each cohort have completed Visit 4 and their data are available for analysis, and before enrollment of the remaining subjects in the respective cohort and before enrollment of the first 5 subjects in the subsequent cohort. In addition, in between the different enrollment stages, the DMC will review all available safety data of subjects that have completed Visit 4 and all available safety data of subjects that have completed Visit 6.

The specific roles and responsibilities of the DMC members and other personnel involved will be documented in the DMC charter. The DMC charter will be finalized before the start of the study and will outline in detail all pausing and stopping rules according to the Clinical Study Protocol.

3.8 Premature Withdrawal from Study

Subjects may withdraw at any time, or be dropped from the study at the discretion of the investigator should any untoward effects occur and/or for safety reasons. In addition, a subject may be withdrawn by the investigator or the Sponsor if he/she violates the study plan or for administrative reasons. The investigator or study coordinator must notify the Sponsor immediately when a subject has been withdrawn due to an adverse event.

The circumstances above are referred to as premature withdrawal from the study, and the reason for premature withdrawal should be clearly documented and detailed in the source documentation. The investigator should make every attempt to evaluate the subject's safety, including resolution of ongoing AEs, at the time of premature withdrawal. If a subject wants to withdraw from the study prior to the last planned study visit, the subject will be asked to be followed for safety for the duration of the study. When a subject withdraws, or is withdrawn, from the study, the procedures described in section 5.5.1 should be completed if possible.

The reasons for premature withdrawal from the study include: Adverse event, death, withdrawal of consent, lost to follow-up, administrative reason, and protocol deviation. These reasons are described in greater detail below.

Adverse Event

For any subject withdrawn from study participation prior to the planned Study Termination Visit, it is important to determine if an AE was associated with the reason for discontinuing the study. This AE must be identified on the appropriate CRF page by indicating "Withdrawn from study due to AE". Any ongoing AEs at the time of study withdrawal must be followed until resolution or stabilization.

Death

For any subject withdrawn from study participation due to death, this should be noted on the appropriate CRF page and the associated SAE that led to the death must be reported.

Withdrawal of consent

The subject can withdraw consent for participation in the study at any time without penalty or loss of benefit to which the subject is otherwise entitled. Reason for early termination should be deemed as "withdrawal of consent" if the subject withdraws from participation due to a non-medical reason (i.e., reason other than AE). If the subject intends to withdraw consent from the study, the investigator should clarify if the subject will withdraw completely from the study or if the subject will continue study participation for safety, or a subset of other study procedures. If the subject requests complete withdrawal from the study, no further study interventions will be performed with the subject.

Lost to Follow-Up

For subjects who fail to show up for study visits (clinic or telephone contacts), study staff is encouraged to make at least three documented attempts to contact the subject by telephone and at least one documented written attempt to contact the subject to encourage the completion of study termination procedures. These efforts to contact the subject must be recorded in the source document. The termination date for the subject to be captured on the appropriate CRF page is the date of the last contact (clinic visit or telephone) with the subject.

Administrative Reason

Examples for subjects withdrawn from the study due to administrative reason can include: Sponsor decision to terminate the study, subject meeting a pre-specified withdrawal criterion, subject discontinuation for insurance issues, moving, no time, etc. This reason should be noted in the appropriate CRF page and any ongoing AEs at the time of study withdrawal must be followed until resolution/stabilization.

If the clinical study is prematurely terminated by the Sponsor, the investigator is to promptly inform the study subjects and local EC/IRB and should assure appropriate therapy and follow up for the subjects. All procedures and requirements pertaining to the archiving of study documents should be followed. All other study materials (study medication/vaccines, etc.) must be returned to the Sponsor.

For subjects who are withdrawn from the study due to receipt of an excluded medication/vaccination or due to significant protocol non-compliance, this reason should be noted in the appropriate CRF page.

Protocol Deviation

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. In general, subjects associated with protocol deviations may remain in the study unless continuation in the study jeopardizes the subject's health, safety, or rights.

Investigators will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact GSK or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a change to the protocol would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by GSK and approved by the IRB/EC and health authorities it cannot be implemented.

Any subject who becomes pregnant during the study should be encouraged to continue participating in the study for safety follow-up. The site must complete a Pregnancy Report CRF (initial report) as soon as possible after learning of pregnancy occurrence (see section 7.1.6 for further details). If the subject withdraws from the study for any of the above categories except death, the site will obtain permission from the subject to continue to remain in contact with her until the outcome of the pregnancy is known, even if the outcome is not known until after the subject reaches the end of the routine study period.

3.9 End of Study

Most clinical trials intended to support the efficacy/immunogenicity and safety of an Investigational Product proceed to full completion of planned sample size accrual.

A subject is considered to have completed this study when he/she has: (1) received the intended dose of study vaccine and (2) completed 365 days (Visit 12) of safety follow-up after receiving the study vaccine.

Evaluation of the primary and secondary immunogenicity objectives requires the testing of biological samples from all study subjects, which can only be completed after all samples are collected. The last samples for the analysis of the primary and/or secondary objectives will be taken at Visit 9 (Day 181). For the purpose of this protocol, End of Study is defined as the completion of the testing of such biological samples, to be achieved no later than 8 months after collection of the last biological sample at Visit 9.

4.0 SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

In order to participate in this study, all subjects must meet all of the inclusion criteria described.

1. Male or female individuals of 18 through 45 years of age on the day of informed consent.
2. Healthy volunteers with good physical and mental health status, determined on the basis of the medical history, a physical examination and the results of the screening tests as judged by the investigator.
3. Individuals who have voluntarily given written informed consent after the nature of the study has been explained according to local regulatory requirements, prior to study entry.
4. Individuals who can comply with study procedures including follow-up[1].
5. Individuals that are able to understand, read and write German language.
6. Females of childbearing potential who are using an effective birth control method[2] which they intend to use for at least 30 days after the study vaccination.

4.2 Exclusion Criteria

Each subject must not have or must not be:

1. Progressive, unstable or uncontrolled clinical conditions.
2. Hypersensitivity, including allergy, to any component of vaccines, medicinal products or medical equipment whose use is foreseen in this study.

[1] A subject is considered to be compliant if the Investigator judges that the subject will complete the Subject Diary, return for all the follow-up visits and be available for telephone calls as scheduled in the study.

[2] The following birth control methods are considered effective:

- Hormonal contraceptive (such as oral, injection, transdermal patch, implant) if used for at least 30 days prior to informed consent
- Diaphragm with spermicide, tubal occlusion device
- Intrauterine device (IUD)
- Tubal ligation
- Male partner using condom with spermicide
- Male partner having been vasectomized at least six months prior to informed consent

3. Clinical conditions representing a contraindication to intramuscular vaccination and blood draws.
4. Abnormal function of the immune system resulting from:
   a. Clinical conditions.
   b. Systemic administration of corticosteroids (PO/IV/IM) for more than 14 consecutive days within 90 days prior to informed consent.
   c. Administration of antineoplastic and prescription immunomodulating agents or radiotherapy within 90 days prior to informed consent.
5. Received immunoglobulins or any blood products within 180 days prior to informed consent.
6. Received an investigational or non-registered medicinal product within 30 days prior to informed consent or intend to participate in another clinical study at any time during the conduct of this study.
7. Vulnerable subjects (e.g. persons kept in detention), study personnel or an immediate family or household member of study personnel, subjects with legal incapacity or limited legal capacity
8. Any relevant deviation from the laboratory parameters at screening as judged by the investigator.
9. Previously received any vaccine that included a MenC antigen.
10. Previously suspected or confirmed disease caused by *N. meningitides.*
11. Had household contact with and/or intimate exposure to an individual with culture proven MenC.

12. A positive serum or urine pregnancy test prior to the study vaccine administration or are currently lactating.

13. A positive drugs-of-abuse test prior to the study vaccine administration

14. Received any other vaccines within 30 days prior to enrolment in this study or who are planning to receive any vaccine within 30 days from the administration of study vaccines.

15. Any other condition that, in the opinion of the investigator, might interfere with the results of the study or pose additional risk to the subject due to participation in the study.

4.3 Criteria for Delay of Vaccination or Blood Draw

There may be instances when individuals meet all eligibility criteria for vaccination or blood draw yet have a transient clinical circumstance which may warrant delay of vaccination or blood draw. Under such circumstances, a subject may be considered eligible for study enrolment after the appropriate window for delay has passed and inclusion/exclusion criteria have been rechecked, and if the subject is confirmed to be eligible.

Reasons for delay of vaccination include:

- Body temperature elevation ≥38.0°C (measured orally) within 3 days prior to intended study vaccination.
- Use of antipyretics and/or analgesic medications within 24 hours prior to vaccination.

Reasons for delay of blood draw include:

- Subject has received a dose of systemic antibiotics less than 6 days before blood collection for the hSBA directed against MenC.

5.0 STUDY PROCEDURES

The sections that follow provide an overview of the procedures that are to be followed in enrolling, evaluating, and following subjects who participate in this clinical study. Visits can be either clinic visits or safety follow-up telephone calls, as specified in the Table below and in the Time and Events Tables 3 and 4 of the Study Synopsis.

Table 5.0-1: Study procedures

Visit Category	Procedures
Pre-vaccination Clinic Visit	Section 5.1 describes procedures to be followed prior to subject enrollment, including: informed consent and screening procedures.
Vaccination Clinic Visit	Section 5.2 describes procedures to be followed during the vaccination clinic visit, including: prevaccination procedures, enrolment, randomization, vaccination and post-vaccination procedures.
Post-vaccination Visits	Section 5.3 describes follow-up clinic visits and safety follow-up calls.
Unscheduled Visits	Section 5.4 describes possible procedures to be followed at unscheduled clinic visit.
Study Termination Visit	Section 5.5 describes procedures to be followed at the last study visit for a subject (may include early termination visit).

5.1 Pre-vaccination Clinic Visit(s)

The Pre-vaccination Clinic Visit must be performed in the period between Day -28 and Day -3.

This section describes the procedures that must be performed for each potential subject prior to enrollment, including obtaining informed consent and screening.

5.1.1 Informed Consent

"Informed consent" is the voluntary agreement of an individual or his/her legal guardian(s) to participate in research. Consent must be given with free will of choice, and without undue inducement. The individual must have sufficient knowledge and understanding of the nature of the proposed research, the anticipated risks and potential benefits, and the requirements of the research to be able to make an informed decision.

Informed consent following local IRB/EC guidance **must** be obtained before conducting any study-specific procedure (i.e., all of the procedures described in the protocol). Prior to any additional blood sample collection for exploratory objectives, a secondary informed consent **must** be signed by subjects. The process of obtaining informed consent should be documented in the subject source document in addition to maintaining a copy of the signed and dated informed consent.

5.1.2 Screening

After an individual has consented to participate in the study and informed consent is signed, that individual will be given a unique Screening Number. The subject's unique Screening Number will be documented in the Screening and Enrolment log. The eligibility of the subject will be determined based on the inclusion and exclusion criteria listed in section 4.0 and evaluated during this screening procedure.

Screening procedures at the Pre-vaccination Clinical Visit (between Day -28 and Day -3) will include the following:

- Review of demographic data, including age, gender, race, body weight and height.
- Review of medical history, including but not limited to any medical history, ongoing illnesses or injuries that may be relevant to subject eligibility for study participation. Relevant medical history can also include any medical history that contributes to the understanding of an adverse event that occurs during study participation, if it represents an exacerbation of an underlying disease/pre-existing problem.
- Perform physical examination, including but not limited to:
  - Assessment of general appearance
  - Collection of vital signs, including body temperature, blood pressure, heart rate and respiratory rate
  - Examination of head, ears, eyes, nose and throat (HEENT)
  - Examination of skin
  - Auscultation of heart and lungs
- Collection and review of prior and concomitant medications or vaccinations taken prior to start of study (refer to section 6.5 for further details).
- Collection of any unsolicited AEs occurring prior to administration of the study vaccine.

- Blood draw (approximately 10 ml) for Safety Laboratory assessments, measurement of Hepatitis B surface antigen, anti-Hepatitis C virus antibodies, anti-HIV 1 and 2 antibodies and serum pregnancy test (all women).
- Urine sample for Safety Laboratory assessments and drugs-of-abuse testing.

NOTE: A general physical examination is to be performed by a qualified health care practitioner. "Qualified health care practitioner" refers to any licensed health care professional who is permitted by institutional policy to perform physical examinations and who is identified within the Study Staff Signature Log.

Data collected during the Pre-vaccination Screening Clinic Visit must be written in the source document (see section 9.1) and will be captured in the screening CRF Forms. In the event that the individual is determined ineligible for study participation, he/she is considered a screen failure. The reason for screen failure must be documented in the Screening and Enrolment log.

5.2 Vaccination Clinic Visit(s)

This section describes the procedures to be performed at the Vaccination Clinic Visit (Visit 1, Day 1), including: pre-vaccination procedures, enrolment, randomization, prevaccination blood draw, vaccination and post-vaccination procedures.

5.2.1 Pre-vaccination Procedures

During pre-vaccination procedures at Visit 1 (Day 1), the eligibility of the subject will be confirmed based on the inclusion and exclusion criteria listed in section 4.0.

Pre-vaccination procedures at Visit 1 (Day 1) will include the following:

- Review of systems by means of a structured interview that queries the subject as to any complaints the subject has experienced across each organ system.
- Perform physical examination, including but not limited to:
  - Assessment of general appearance
  - Assessment of body weight and collection of vital signs, including body temperature, blood pressure, heart rate, and respiratory rate
  - Examination of head, ears, eyes, nose and throat (HEENT)
  - Examination of skin
  - Auscultation of heart and lungs

- Collection and review of prior and concomitant medications or vaccinations taken, or recalled, since the last visit (refer to section 6.5 for further details).
- Collection of any unsolicited AEs occurring prior to administration of the study vaccine.
- One blood sample (approximately 10 ml) will be drawn from all subjects for serology testing.
- One blood sample (approximately 10 ml) will be drawn from all subjects for baseline Safety Laboratory assessments.
- One urine sample for baseline Safety Laboratory assessments, pregnancy testing (all women) and drugs-of-abuse testing.
- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and volume of blood draws are provided in section 3.5.

NOTE: A general physical examination is to be performed by a qualified health care practitioner. "Qualified health care practitioner" refers to any licensed health care professional who is permitted by institutional policy to perform physical examinations and who is identified within the Study Staff Signature Log.

Data collected during pre-vaccination procedures at Visit 1 must be written in the source document (see section 9.1). In the event that the individual is determined ineligible for study participation, he/she is considered a screen failure. The reason for screen failure must be documented in the Screening and Enrolment log. If the individual is determined to be eligible for the study, he/she can be enrolled into the study.

5.2.2 Enrolment

After an individual is determined to be eligible for study participation, the investigator will enroll the subject into an Electronic Data Capture (EDC) system where the randomization to the treatment group will occur. The Screening Number ceases to be used and remains in the Screening and Enrolment Log only.

If for any reason, after signing the informed consent form (ICF), the subject who is eligible and enrolled fails to be randomized, this is called a randomization failure. In this case the early termination study procedures must be applied. The reason for all randomization failures should be recorded in the Screening and Enrolment Log and in the source document as specified in the Source Data Agreement. The information on subjects

who are randomization failures should be kept distinct from subjects who are screen failures, as described in section 5.1.2 and section 5.2.1.

5.2.3 Randomization

Enrolled subjects will be randomized and automatically assigned a unique Subject ID. The Subject ID will be the subject's unique identification number for all CRFs and associated study documentation that will be used for the duration of the study.

If for any reason, after signing the informed consent form (ICF), the eligible subject is enrolled and randomized but fails to undergo treatment, this is an Early Termination and the reason should be recorded in source document as specified in the Source Data Agreement/Source Data Verification Form. The information on these Early Termination subjects should be kept distinct in the source documentation from randomization failures, which are described in section 5.2.2.

5.2.4 Vaccination

After completing the pre-vaccination procedures at Visit 1 (Day 1), administer the vaccine to the subject according to the procedures described in section 6.3. Observe the blinding procedures described in section 3.3.

5.2.5 Post-vaccination Procedures

The following post-vaccination procedures will be performed at Visit 1 (Day 1):

- After vaccination, the subject will be observed for at least 30 minutes for any immediate solicited and unsolicited AEs and a body temperature measurement at 30 min after vaccination. All safety and body temperature data collected during this time are to be recorded in the subject's source document.
- After vaccination, the subject will be observed for at least 24 hours at the clinic including observation for solicited and unsolicited AEs and body temperature measurements. Body temperature measurements must be performed at 2, 4, 6, 8, 10, 12, 18 and 24 hours after vaccination. All safety and body temperature data collected during this time are to be recorded in the subject's source.
- One blood sample (approximately 10 ml) will be drawn from all subjects at 24 hours after vaccination for Safety Laboratory assessments.
- One urine sample will be collected from all subjects at 24 hours after vaccination for Safety Laboratory assessments.

- From those subjects that signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn in the first 24 hours after vaccination. Details regarding the number and volume of post-vaccination blood draws are provided in section 3.5.

After the initial 24 hours inpatient observation period, a Subject Diary will be used in this study to document solicited and unsolicited AEs until Day 14. The Subject Diary is the only source for collection of solicited AEs after the initial 24 hours inpatient observation period. Therefore, it is critical that the subject completes the Subject Diary correctly.

The following training regarding completion of the Subject Diary must be provided:

- The subject should be trained on how and when to complete each field of the Subject Diary.
- The subject should be trained on how to self-measure local solicited adverse events and body temperature. The measurement of solicited local adverse events is to be performed using the ruler provided by the site.
- The subject should be instructed how to perform body temperature measurement using the thermometer provided by the site. If the subject feels unusually hot or cold during the day, the subject should check their body temperature. If the subject has fever, the highest body temperature observed that day should be recorded in the Subject Diary.

Subject Diary training should be directed at the individual(s) who will perform the measurements of adverse events and who will enter the information into the Subject Diary. This individual may not be the subject, but if a person other than the subject enters information into the Subject Diary, this person's identity must be documented in the Subject Diary. Any individual that writes in the Subject Diary must receive training on completion of the Diary Card at the time of the visit. This training must be documented in the subject's source record.

The site should schedule the next study activity (clinic visit) with the subject.

The subject will receive a written reminder of the next planned study activity. The subject will be reminded to complete the Subject Diary and to contact the site if there are any questions, and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

5.3 Post-vaccination Visit(s)

5.3.1 Subject Diary Reminder, Safety Follow-up and/or Post-vaccination Blood Draw Clinic Visits

Subject Diary reminder, Safety follow-up and/or post-vaccination blood draw clinic visits will be performed on Day 4 (Visit 2), Day 8 (Visit 3), Day 15 (Visit 4), Day 29 (Visit 6), Day 85 (Visit 7), Day 113 (Visit 8) and Day 181 (Visit 9)

At Day 4 (Visit 2) the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. All unsolicited AEs, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. Any concomitant medications or vaccinations associated with those events must also be recorded on the source documents.
- All subjects will be reminded to complete the Subject Diary and to contact the site if there are any questions, and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit. No changes to the Subject Diary should be done at the clinic visit.
- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and volume of blood draws are provided in section 3.5.
- The site should schedule the next study activity (clinic visit) with the subject and the subject will receive a written reminder of the next planned study activity.

At Day 8 (Visit 3) the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. All unsolicited AEs, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. Any concomitant medications or vaccinations associated with those events must also be recorded on the source documents.

- The subject will be reminded to complete the Subject Diary and to contact the site if there are any questions, and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to hospitalization or an emergency room visit. No changes to the Subject Diary should be done at the clinic visit.
- Blood draw (approximately 10 ml) from all subjects for Safety Laboratory assessments.
- Urine sample from all subjects for Safety Laboratory assessments.
- Blood draw (approximately 10 ml) from all subjects for serology testing.

- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and
- volume of blood draws are provided in section 3.5.

  The site should schedule the next study activity (clinic visit) with the subject and the subject will receive a written reminder of the next planned study activity.

At Day 15 (Visit 4) the following procedures will be performed:

- The Subject Diary will be collected and reviewed. No changes to the Subject Diary should be done at the clinic visit. For details on the Subject Diary see sections 3.4.2, and 5.2.5. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. All unsolicited AEs until Day 14, solicited local and systemic AEs persisting at Day 14, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. All concomitant medications or vaccinations associated with those events must also be recorded on the source documents.
- The site should schedule the next study activity (safety phone call) with the subject.
- The subject will receive a written reminder of the next planned study activity. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

At Day 29 (Visit 6) the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. Any solicited local and systemic AEs continuing beyond Day 14, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. All concomitant medications or vaccinations associated with those events must also be recorded on the source documents.

- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and

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- Blood draw (approximately 10 ml) from all subjects for Safety Laboratory assessments.
- Urine sample from all subjects for Safety Laboratory assessments.
- Blood draw (approximately 10 ml) from all subjects for serology testing.

volume of post-vaccination blood draws are provided in section 3.5.

The site should schedule the next study activity (clinic visit) with the subject.

- The subject will receive a written reminder of the next planned study activity. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

At Day 85 and Day 113 (Visit 7 and Visit 8), the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. Any solicited local and systemic AEs continuing beyond Day 14, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. All concomitant medications or vaccinations associated with those events must also be recorded on the source documents.
- The site should schedule the next study activity (clinic visit) with the subject.
- The subject will receive a written reminder of the next planned study activity. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

At Day 181 (Visit 9), the following procedures will be performed:

- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and

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- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. Any solicited local and systemic AEs continuing beyond Day 14, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. All concomitant medications or vaccinations associated with those events must also be recorded on the source documents.
- Blood draw (approximately 10 ml) from all subjects for serology testing.

  volume of post-vaccination blood draws are provided in section 3.5.

  The site should schedule the next study activity (safety phone call) with the subject.
- The subject will receive a written reminder of the next planned study activity. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

5.3.2 Safety Follow-up Calls

Safety follow-up calls will be performed on Day 22 (Visit 5), Day 209 (Visit 10) and Day 271 (Visit 11) and include the following procedures:

- Safety follow-up calls are calls made to the subject by a healthcare professional designated on the site log. These calls will follow a script which will facilitate the collection of relevant safety information. The subject will be interviewed according to the script, and information relating to solicited local and systemic AEs persisting beyond Day 14 and unsolicited adverse events including SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal, and/or NOCD and concomitant medications or vaccinations associated with those events. All safety information described by the subject must be written down in a designated location within the source document and not written on the script used for the telephone call.

- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and

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- The site should schedule the next study activity (clinic visit or study termination visit) with the subject.
- The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

5.4 Unscheduled Visits

An unscheduled visit describes a non-routine study visit triggered by a specific event. These could include anticipated or unanticipated adverse events or interventions.

The following procedures should be carried out for all unscheduled visits:

1. Evaluate the subject's vital signs body temperature, heart rate, and blood pressure and perform a symptom-directed physical examination.
2. Record any observed AEs in the source documents.

3. Record any concomitant medications or vaccinations associated with AEs in the source documents.

5.5 Study Termination Visit

The study termination visit is scheduled on Day 366 (Visit 12). The termination visit is a clinic visit. For visit procedures to be performed for a subject whose planned study participation ends prematurely, please see section 5.5.1.

At the Study Termination clinic visit the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit.
- The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present.
- Medically attended AEs, SAEs, NOCDs, or AESIs will be recorded on source documents.
- All medications taken or vaccines received will also be recorded on the source documents.
- The site will review with the subject the plan of when information relating to the subject's participation in the study may be available (e.g., study results, treatment assignments). It will also be discussed how information relating to the subject's participation in the study will be shared with the subject's healthcare provider, if the subject chooses to share this information.
- The site will complete the termination CRF page and this will mark the completion of the subject's participation in the study.

5.5.1 Early Termination Visit

The date of termination is the date of the last contact in which the subject's health status was assessed or, in cases where the subject does not agree to any further safety follow-up, it is the date consent is withdrawn. This date should be recorded on the appropriate CRF page.

When a subject is withdrawn from treatment or withdraws from the study, the investigator will notify the Sponsor and, when possible, will perform the procedures listed below.

The reason(s) for the early termination must be included in the subject's source documentation. If the Early Termination Visit is a telephone call, collect as much information as possible. Early Termination Visits include subjects who were randomized but not treated.

At the clinic visit or during the telephone call, the following procedures should be performed, when possible:

- Collection and review of Subject Diary (if not already collected).
- Interview of subject to collect unsolicited adverse events, medically attended AEs, AEs leading to withdrawal, SAEs, AESIs, and NOCD.
- Interview of subject to collect concomitant medications and/or vaccinations.
- Symptom-directed physical assessment, at least including measurement of vital signs (body temperature, respiratory rate, blood pressure, heart rate) and a check of general appearance (in case of clinic early termination visit).
- Draw a blood sample (approximately 10 ml) and a urine sample for Safety Laboratory assessment (in case of clinic early termination visit).
- The site will review with the subject the plan of when information relating to the subject's participation in the study may be available (e.g., study results, treatment assignments). It will also be discussed how information relating to the subject's participation in the study will be shared with the subject's healthcare provider, if the subject chooses to share this information.
- The site will complete the appropriate CRF page and this will mark the completion of the subject's participation in the study.

6.0 TREATMENT OF SUBJECTS

All vaccines associated with this study are to be stored separately from other vaccines and medications in a secure location under appropriate storage conditions with temperature monitoring. **All vaccines associated with this study must be checked for expiration date prior to use. Expired vaccines must not be administered to subjects.**

6.1 Study Vaccine(s)

The term 'study vaccine' refers to those vaccines provided by the Sponsor, which will be evaluated as part of the study objectives. The study vaccines specific to this study are described in Table 6.1-1.

Table 6.1-1: Study Vaccine Composition

Group A (Control) Meningococcal C-CRM$_{197}$ Conjugate Vaccine	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM$_{197}$ protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
Sodium Chloride	3.5 mg
Sterile water for injection, up to	0.5 ml

Group B (12.5µg LHD153R) - MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM$_{197}$ protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide/LHD153R Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
LHD153R	12.5 µg
Sodium Chloride	3.4 mg

Histidine	0.1 mg
Tris	30 µg
Sterile water for injection, up to	0.5 ml
Group C (25 µg LHD153R) - MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM$_{197}$ protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide/LHD153R Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
LHD153R	25 µg
Sodium Chloride	3.4 mg
Histidine	0.2 mg
Tris	61 µg
Sterile water for injection, up to	0.5 ml

Group D (50µg LHD153R) - MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM$_{197}$ protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg

Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide/LHD153R Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
LHD153R	50 µg
Sodium Chloride	3.2 mg
Histidine	0.4 mg
Tris	121 µg
Sterile water for injection, up to	0.5 ml
Group E (100µg LHD153R) - MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM$_{197}$ protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide/LHD153R Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
LHD153R	100 µg
Sodium Chloride	2.9 mg
Histidine	0.8 mg
Tris	243 µg
Sterile water for injection, up to	0.5 ml

6.2 Non-Study Vaccines

The term 'non-study vaccine' refers to those vaccines which will be intentionally given to study subjects but not formally included in the analysis of study objectives.

No non-study vaccines are planned for this study. Any non-study vaccines administered during the study conduct will be captured in the CRF as concomitant medications and/or vaccinations.

6.3 Vaccine Preparation and Administration

The investigator or designee will be responsible for oversight of the administration of vaccine to subjects enrolled in the study according to the procedures stipulated in this study protocol. All vaccines will be administered only by unblinded personnel who are qualified to perform that function under applicable local laws and regulations for the specific study site.

The vaccine components will be provided in 5 separate kits (i.e. one for the control and one for each of the 4 dosage groups). The vaccine components must be mixed prior to vaccination taking into account the appropriate aseptic procedures. Detailed vaccine preparation and administration instructions, including the maximal administration period, will be provided to investigators prior to study start and must be filed in the Investigator Site File.

PRECAUTIONS TO BE OBSERVED IN ADMINISTERING STUDY VACCINE:

- Prior to vaccination, subjects must be determined to be eligible for study vaccination and it must be clinically appropriate in the judgment of the investigator to vaccinate. Eligibility for vaccination prior to first study vaccine administration is determined by evaluating the entry criteria outlined in protocol sections 4.0.

- Study vaccines must not be administered to individuals with known hypersensitivity to any component of the vaccines.

- Standard immunization practices are to be observed and care should be taken to administer the injection intramuscularly. Before administering vaccine, the vaccination site is to be disinfected with a skin disinfectant (e.g., 70% alcohol). Allow the skin to dry. **DO NOT inject intravascularly**.

- As with all injectable vaccines, trained medical personnel and appropriate medical treatment must be readily available in case of anaphylactic reactions following vaccine administration. For example, epinephrine 1:1000, diphenhydramine, and/or other medications for treating anaphylaxis should be available.

6.4 Vaccine Administration Error or Overdose of Vaccine

Vaccine administration error is defined as receiving a dose of study vaccine that was not reconstituted as instructed or administered by a different route from the intended route of administration. An overdose of study vaccine (whether accidental or intentional) is defined when a dosage higher than the recommended dosage is administered in one dose of study vaccine.

Any vaccine administration error or overdose of study vaccine detailed in this protocol must be reported as an adverse event, and if the vaccine administration error or overdose is associated with a serious adverse event, it must be reported as such within 24 hours to the Sponsor.

6.5 Prior and Concomitant Medications and Vaccines

All medications, vaccines and blood products taken or received by the subject within 180 days prior to the start of the study are to be recorded in the appropriate CRF.

Medications taken for prophylaxis are those intended to prevent the onset of symptoms. Medications taken for treatment are intended to reduce or eliminate the presence of symptoms that are present.

NOTE: Use of antipyretics/analgesics within 24 hours prior to vaccine administration is a reason to delay study vaccination (see section 4.3).

Concomitant medications include all medications (including vaccines) taken by/administered to the subject at and after enrolment and must be documented in the appropriate CRF.

When recording concomitant medications/vaccines, they should be checked against the study entry criteria in section 4.0, to ensure that the subject should be enrolled in the study.

6.6 Vaccine Supply, Labeling, Storage and Tracking

The Sponsor will ensure the following:

- Supply the study vaccines.
- Appropriate labeling of all study vaccines provided that complies with the legal requirements of each country where the study is to be performed.

The investigator must ensure the following:

- Acknowledge receipt of the study vaccines by a designated staff member at the site, including:
  - Confirmation that the vaccines were received in good condition
  - Confirmation to the Sponsor of the temperature range during shipment from the Sponsor to the investigator's designated storage location
  - Confirmation by the Sponsor that the vaccines are authorized for use.
- Proper storage of the study vaccines, including:
  - Storage in a secure, locked, temperature-controlled location.
  - Proper storage according to the instructions specified on the labels.
  - Appropriate record keeping and inventory of the study vaccines, including regular documentation of adequate storage temperature.
- Appropriate use of the study vaccines, including:
  - No use of vaccines prior to receipt of authorization for use from the Sponsor.
  - Use only in accordance with the approved protocol.
  - Proper handling, including confirmation that the vaccine has not expired prior to administration.
  - Appropriate documentation of administration of vaccines to study subjects including:
    - Date, dosage, batch/lot numbers, expiration dates, unique identifying numbers assigned to subjects and study vaccines, and time of vaccine administration. This information will be maintained in an accountability log that will be reviewed by the site monitor.
    - Reconciliation of all vaccines received from the Sponsor. Reconciliation is defined as maintaining records of which and how many vaccines were received, which vaccines were administered to subjects, which vaccines were destroyed at the site, and which vaccines were returned to the Sponsor, as applicable.
- Proper adherence to the local institutional policy with respect to destruction of study vaccines.

- Complete record keeping of vaccine use, wastage, return or destruction, including documentation of:
  - Copy of the site's procedure for destruction of hazardous material.
  - Number of doses destroyed, date of destruction, destruction code (if available), method of destruction, and name of individual performing destruction.

Vaccines that have been stored differently from the manufacturer's indications **must not** be used unless the Sponsor provides written authorization for use. In the event that the use cannot be authorized, the Sponsor will make every effort to replace the vaccine supply. All vaccines used in conjunction with this protocol must be stored separately from normal hospital/practice stocks to prevent unintentional use of study vaccines outside of the clinical study setting.

Monitoring of vaccine accountability will be performed by the study monitor during site visits and at the completion of the study.

At the conclusion of the study, and as appropriate during the course of the study, the investigator must ensure that all unused study vaccines, packaging and supplementary labels are destroyed locally (upon approval from Sponsor) or returned to the Sponsor.

7.0 ASSESSMENTS

7.1 Safety Assessment

The measures of safety used in this study are based on previous study data and based on comparable routine clinical/laboratory procedures. They include a close vigilance for, and stringent reporting of selected local and systemic adverse events routinely monitored in vaccine studies as indicators of reactogenicity.

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

The period of observation for AEs extends from the time the subject signs informed consent until he or she completes the specified safety follow-up period (Day 366) or terminates the study early (whichever comes first). AEs occurring after the informed consent form is signed but prior to receiving study vaccine/product will be documented as an adverse event and recorded within the source documents. However, any AEs occurring prior to receipt of any study vaccine will be analyzed separately from “treatment emergent” AEs (AEs occurring after administration of the first study vaccine).

Adverse events are collected as either solicited or unsolicited adverse events. Solicited events are derived from organized data collection systems, such as Subject Diaries or interview.

7.1.1 Solicited Adverse Events

The term “reactogenicity” refers to solicited signs and symptoms (“solicited adverse events”) occurring in the hours and days following a vaccination, to be collected by the subject after the first 24 hours inpatient observation period at Day 1until Day 14, using a pre-defined Subject Diary.

The following solicited adverse events are included in the Subject Diary. Each adverse event is to be assessed using the scoring system shown in Appendix A (Solicited Local AEs) and Appendix B (Solicited Systemic AE):

Solicited Local Adverse Events

Solicited local AEs include:

- injection site erythema
- injection site induration
- injection site pain
- injection site swelling **Solicited Systemic Adverse Events**

Solicited systemic AEs include:

- body temperature ≥38.0°C (as measured orally)
- loss of appetite
- nausea
- fatigue
- generalized myalgia
- generalized arthralgia
- headache
- chills
- vomiting
- diarrhea
- generalized rash
- urticaria

Other Solicited Data

Other solicited data collected per Subject Diary include:

- Use of analgesics/antipyretics recorded as “absent” or “present” and summarized by “for treatment” or “for prophylaxis”
- Body temperature as recorded daily, ideally at same time, by the oral route

The study staff must review the data entered into the Subject Diary as described in sections 3.4.2 and 5.3.1.

NOTE: Any solicited adverse event that meets any of the following criteria must be entered into the subjects' source documents (see section 9.1) and also as an adverse event in the appropriate CRF:

- Solicited local or systemic adverse event that continues beyond Day 14 after vaccination.
- Solicited local or systemic adverse event that leads to a visit to a healthcare provider (medically attended adverse event, see section 7.1.3).
- Solicited local or systemic adverse event leading to the subject withdrawing from the study or the subject being withdrawn from the study by the investigator (adverse event leading to withdrawal, see section 7.1.3).
- Solicited local or systemic adverse event that otherwise meets the definition of a serious adverse event (see section 7.1.4).

7.1.2 Unsolicited Adverse Events

An unsolicited adverse event is an adverse event that was not solicited using a Subject Diary and that was spontaneously communicated by a subject who has signed the informed consent.

7.1.3 Evaluation of Adverse Events

Every effort should be made by the investigator to evaluate safety information reported by a subject for an underlying diagnosis and to capture this diagnosis as the event in the AE page. In other words, the practice of reporting only symptoms (e.g., "cough" or "ear pain") are better reported according to the underlying cause (e.g., "asthma exacerbation" or "otitis media").

The severity of events reported on the appropriate CRF page will be determined by the investigator as:

Mild: transient with no limitation in normal daily activity.
Moderate: some limitation in normal daily activity.
Severe: unable to perform normal daily activity.

The relationship of the study treatment to an AE will be determined by the investigator based on the following definitions:

1. Not Related

The AE is not related to an investigational vaccine if there is evidence that clearly indicates an alternative explanation. If the subject has not received the vaccine, the timing of the exposure to the vaccine and the onset of the AE are not reasonably related in time, or other facts, evidence or arguments exist that reasonably suggest an alternative explanation, then the AE is not related.

2. Possibly Related

The administration of the investigational vaccine and AE are considered reasonably related in time and the AE could be explained by exposure to the investigational vaccine or by other causes.

3. Probably Related

Exposure to the investigational vaccine and AE are reasonably related in time and no alternative explanation has been identified.

The relationship of the study treatment to an unsolicited AE will be determined by the investigator.

Note: solicited AEs will not be evaluated for relationship to study treatment. Grading for severity of solicited local and systemic AEs is described in Appendix A and Appendix B.

Adverse events will also be evaluated by the investigator for the co-existence of any of the other following conditions:

- "Medically attended adverse event": an adverse event that leads to a visit to a healthcare provider.
- "New onset of chronic disease" (NOCD): an adverse event that represents a new diagnosis of a chronic medical condition that was not present or suspected in a subject prior to study enrolment.
- AEs leading to withdrawal: adverse events leading to study or vaccine withdrawal.

All AEs, regardless of severity, will be monitored until resolution or until the investigator assesses them as chronic or stable. All subjects experiencing AEs - whether considered associated with the use of the study vaccine or not - must be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible.

7.1.4 Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose results in one or more of the following:

- Death.
- Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe.
- Required or prolonged hospitalization.
- Persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions).
- Congenital anomaly/or birth defect.
- An important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

Adverse events which do not fall into these categories are defined as non-serious.

It should be noted that a severe adverse event need not be serious in nature and that a serious adverse event need not, by definition, be severe.

Serious adverse events will be captured both on the Vaccines Serious Adverse Event (VSAE) form as well as on the appropriate CRF page. All SAEs will be evaluated by the investigator for relationship of the event to study vaccine. SAEs that are judged to be possibly or probably related to the study vaccine should be reported to the Sponsor as related/suspected events.

The relationship of the study treatment to an SAE will be determined by the investigator based on the following definitions:

1. Related/suspected

The SAE is judged by the investigator to be possibly or probably related to the study vaccine on the appropriate CRF page (see section 7.1.3).

2. Not Related

The SAE is not related if exposure to the study vaccine has not occurred, **or** the occurrence of the SAE is not reasonably related in time, **or** the SAE is considered unlikely to be related to use of the study vaccine, i.e., there are no facts (evidence) or arguments to suggest a causal relationship.

The relationship of the study vaccine to an SAE will be determined by the investigator.

In addition, SAEs will be evaluated by the Sponsor or designee for "expectedness." An unexpected AE is one that is not listed in the current Summary of Product Characteristics or the Investigator's Brochure or an event that is by nature more specific or more severe than a listed event.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the appropriate CRF. If the onset of an event occurred before the subject entered the study (e.g., any pre-planned hospitalization for conditions like cosmetic treatments or for non-emergency routine visits for a pre-existing condition), the hospitalization would not lead to an AE being classified as serious unless, in the view of the investigator, hospitalization was prolonged as a result of participation in the clinical study or was necessary due to a worsening of the pre-existing condition.

7.1.4.1 Adverse Events of Special Interest

Certain adverse events of special interest (AESIs) are monitored after the administration of immunostimulatory agents. All subjects enrolled in this study will be monitored for AESIs for the entire follow-up period. The AESIs will be defined according to MedDRA preferred terms. The investigator will be provided with a list of AESIs prior to study start. Receipt of this list will be notified and stored, along with the list of AESIs, in the Investigator Site File. During the course of the trial the list of AESIs may change. If this occurs, the investigators will be advised of the change and confirmation of receipt will be documented. The updated list of AESIs and documentation of receipt are also stored in the Investigator Site File. The occurrence of any of these adverse events will be treated as a serious adverse event (SAE), meeting the criterion of a "medically important event."

Subjects will be assessed for diagnosis of an AESI at the following visits:

- Pre-vaccination clinic visit (Day -28 to Day -3)
- Visit 1 (Day 1, pre-vaccination)
- Visit 2 (Day 4)

- Visit 3 (Day 8)
- Visit 4 (Day 15)
- Visit 5 (Day 22; Safety Follow-Up Call)
- Visit 6 (Day 29)
- Visit 7 (Day 85)
- Visit 8 (Day 113)
- Visit 9 (Day 181)
- Visit 10 (Day 209; Safety Follow-Up Call)
- Visit 11 (Day 271; Safety Follow-Up Call)
- Visit 12 (Day 366; Study Termination Visit)

At these visits a qualified health care practitioner listed on the site's responsibilities and delegation logs will conduct a review of organ systems and a targeted physical exam and will evaluate subjects for any new signs or symptoms that could indicate one of the AESIs as specified in the list of AESIs stored in the Investigator Site File. They will also interview the subject about recent medical history and any new diagnosis that could indicate an AESI. Medical records related to any new medical event or diagnosis will be requested, reviewed by the site staff, and recorded in the subject's source documents.

A diagnosis of an AESI will be reported in the same manner and time frame as an SAE using the VSAE form. The investigator must notify GSK within 24 hours. The AESI diagnosis, as well as any medications taken to treat the condition, will be recorded in the subject's source documents and on the appropriate CRF.

7.1.5 Methods for Recording Adverse Events and Serious Adverse Events

All findings regarding Adverse Events must be reported on the appropriate CRF page and on the VSAE form, if applicable, which is part of the Investigator Site File. All findings in subjects experiencing AEs must be reported also in the subject's source document.

All SAEs which occur during the course of the study, whether considered to be associated with the study vaccination or not, must be reported **within 24 hours of the site becoming aware of the event** to GSK or its designee. Specific instructions and contact details for collecting and reporting SAEs to GSK will be provided to the investigator.

All SAEs are also to be documented on the appropriate CRF page. Any medication or other therapeutic measures used to treat the AE will be recorded on the appropriate CRF(s) in addition to the outcome of the AE.

After receipt of the initial report, representatives of GSK or its designee will contact the investigator if it is necessary to obtain further information for assessment of the event.

All SAEs must be reported by the investigator to his/her corresponding EC and applicable regulatory authorities in accordance with institutional policy/regulatory requirements and adequate documentation of this notification must be provided to the Sponsor.

GSK or its designee must also comply with the applicable regulatory requirement(s) related to the reporting of suspected unexpected serious adverse vaccine reactions (also known as SUSARs) to the regulatory authority(ies) and the IRB/EC. If a SUSAR or other safety signal relating to use of one of the study vaccines is reported to GSK or its designee, the Sponsor will communicate the information to the investigator and the investigator will be responsible for submitting this information to the EC and other relevant authorities.

7.1.5.1 Post-Study Events

Any suspected SAE that occurs outside of the protocol-specified follow-up period or after the end of the study but considered to be caused by the study vaccine must be reported to GSK or its designee. These SAEs will be processed by GSK or its designee as during the course of the study, until 3 months after the last scheduled study visit. Instructions and contact details for collecting and reporting these suspected SAEs will be provided to the investigator.

7.1.6 Pregnancies

To ensure subjects' safety, each pregnancy in a subject after study vaccination must be reported to GSK within 72 hours of the site learning of its occurrence. If the subject agrees to submit this information, the pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if intended duration of safety follow-up for the study has ended.

Pregnancy data must be recorded on a Pregnancy Report CRF (initial report) and Pregnancy Follow-Up CRF (outcome report).

Any pregnancy outcome meeting the definition of a SAE (see section 7.1.4) must also be reported on the VSAE Report Form.

7.1.7 Safety Laboratory Measurements

Blood and urine samples will be collected from all subjects at the Pre-vaccination Screening, at Visit 1 (pre-vaccination and 24 hours after vaccination), at Visit 3 and at Visit 6 as outlined in Time and Events Table 3. The blood safety laboratory assessments will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, liver function tests (ALT, AST), a complete blood count and C-reactive protein. The urine safety laboratory assessments will include protein, glucose and red blood cells. An additional blood and urine sample will be collected in case of a clinic Early Termination Visit as outlined in section 5.5.1.

All testing will be conducted by qualified and certified laboratories. The Investigator **must** assess all safety laboratory results. Abnormal laboratory values must be classified by the Investigator as clinically significant or not. Abnormal laboratory values that are considered clinical significant will be defined following the FDA CBER Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" dated September 2007, or the institution's normal ranges if they differ from CBER guidance. Please see Appendix C, D and E for further details on the Toxicity Grading Scales according to CBER.

Retesting may be performed in case of abnormal values per guidance of the investigator.

7.2 Efficacy Assessment

Efficacy measurement will not be performed as part of this study.

7.3 Immunogenicity Assessment

The measures to assess the primary and secondary immunogenicity endpoints for this study are standard, i.e., widely used and generally recognized as reliable, accurate, and relevant (able to describe the quality and extent of the immune response).

The assay's used in this study to assess the primary and immunogenicity endpoints are human serum bactericidal assay (hSBA) and ELISA specific for MenC

The hSBA is a functional measure of the ability of specific antibodies, in conjunction with human complement, to kill MenC indicator strains, and is widely used and generally recognized as the serological correlate of protection. The specific ELISA will be used to

measure the induction of antibodies directed against MenC following vaccination with the study vaccines.

Blood samples (approximately 10 ml) to obtain serum for hSBA and ELISA assays will be collected at Day 1, Day 8, Day 29 and Day 181 (refer to section 3.5 for detailed specimen collection procedures).

Testing will be conducted by a GSK or designated laboratory in a blinded manner towards the treatment group. Laboratory contact details are listed in the Protocol Ancillary Document.

All data will be captured at the laboratory and transferred via Electronic Data Transfer (EDT)

Details on all blood sample handling steps are described in the Clinical Specimen Lab Manual provided to the study site.

7.4 Exploratory Measurements

In those subjects who agree to a separate Informed Consent, additional blood samples will be collected at Day 1, Day 4, Day 8, Day 29 and Day 181 for exploratory measurements. The purpose of these exploratory measurements is to assess the systemic exposure of LHD153, to further delineate vaccine induced antigen specific immune responses and to evaluate biomarkers that may be predictive for safety and/or innate immune activation.

All exploratory measurements will be conducted by a GSK or a designated laboratory. Laboratory contact details are listed in the Protocol Ancillary Document.

Exploratory measurements may be performed after the Clinical Study Report (CSR) has been completed, in which case these data will be submitted as an addendum to the CSR.

Systemic exposure of LHD153

Systemic exposure of LHD153 will be assessed by analyzing LHD153 blood plasma levels at Day 1 (baseline, 1, 2, 4, 8 and 24h after vaccination) and Day 4 using LC/MS/MS. Time-points for assessment of clinical exposure of LHD153 have been selected based on non-clinical data in dogs and rats.

Vaccine-induced antigen-specific immune responses

The frequency of B cells specific for MenC polysaccharide and CRM_{197} will be determined by enzyme-linked immunosorbent spot (ELISPOT) at Day 1, Day 8, Day 29 and Day 181 in order to evaluate the baseline specific B-cell frequency (Day 1), the peak

of plasmablast responses (Day 8), the peak of B cell memory responses (Day 29), and the persistence of memory B cell responses (Day 181).

Subsequently, the diversity of the antigen specific B-cell repertoire as well as the specific antibody functionality will be analyzed in a selected subset of subjects. The selection of the subset will be based on the most pronounced response to the study vaccines when compared to baseline as determined by the primary and secondary immunogenicity assessment.

The diversity of the elicited B-cell receptors will be assessed through sequence analysis of complementary DNA (cDNA) generated from immunoglobulin (Ig) messenger RNA (mRNA). The Ig cDNAs will be analyzed from antigen-specific B cells obtained at Day 1, Day 29 and/or Day 181 and plasmablasts isolated at Day 8. The analysis of the B-cell receptor diversity does not have the intent nor the capability to identify or rule out any genetic modifications in the RNA or DNA that are presumably linked to disease or predisposition to disease.

To evaluate the functionality specific antibodies induced by the study vaccines, biochemical and cell-based assays will be performed on a selected subset of serology samples collected for the assessment of the primary and secondary immunogenicity endpoints at Day 1, Day 8, Day 29 and Day 181. The evaluation of antigen specific antibody functionality includes determination of the antibody isotype and the antibody glycosylation state. Furthermore, the ability of the MenC-specific antibodies to fix complement, to promote antibody-dependent cell mediated cytoxicity (ADCC), to induce phagocytosis and to activate FcR+ cells in vitro will be assessed. If the quantity of serum available for this specific exploratory objective is limited, assessments of isotype and glycosylation state will be prioritized over the other assessments.

The frequency of T cells specific for the CRM_{197} protein at baseline (Day 1), at Day 8 and at Day 29 after vaccination with the study vaccines will be determined by FACS analysis using intracellular staining with a panel of cytokines and surface markers to identify cell populations.

Early Markers for Safety and Innate immune activation

The evaluation of potential biomarkers of safety and innate immune activation will be performed on blood specimens collected at Day 1 (baseline, 6h and 24h after vaccination) and Day 4.

The vaccine-induced production of inflammatory cytokines and chemokines will be monitored on serum samples using a commercially available electrochemoluminescence assay for a panel of pro-inflammatory cytokines and chemokines, including Eotaxin,

Eotaxin-3, GM-CSF, IFN-g, IL-1a, IL-1b, IL-10, IL-12 p70, IL-12/IL-23p40, IL-13, IL15, IL-16, IL-17A, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-8 (HA), IP-10, MCP-1, MCP-4, MDC, MIP-1a, MIP-1b, TARC, TNF-a, TNF-b, VEGF.

The vaccine-induced expression of genes and gene families will be monitored on whole blood samples using of RNA microarrays by existing technologies. The RNA micro array analysis does not have the intent nor the capability to identify or rule out any genetic modifications in the RNA or DNA that are presumably linked to disease or predisposition to disease.

The vaccine-induced changes in myeloid (e.g. monocytes and dendritic cells) and lymphoid (e.g. NK cells, NKT cells) cell numbers and their activation status will be assessed using flow cytometry.

8.0 STATISTICAL CONSIDERATIONS

8.1 Endpoints

8.1.1 Primary Endpoint(s)

8.1.1.1 Primary Safety Endpoint(s)

The measures for assessing safety and tolerability (by vaccine group within each cohort and by LHD153R adjuvant dosage group overall) are as follows:

- The frequency and percentage of subjects with solicited local and systemic AEs through Day 14. Time intervals after vaccination that will be summarized are:30 minutes post-vaccination, Days 1-4 (without 30 minutes), Days 5-8, Days 8-14, Days 1-8 (without 30 minutes) and Days 1-14 (without 30 minutes).
- The frequency and percentage of subjects with any unsolicited AEs from the day of vaccination (Day 1) to Day 14.
- The frequency and percentage of subjects with SAEs, medically attended AEs, AEs leading to study withdrawal, NOCDs, AESIs for the following time periods: day of signed informed consent until study completion (Day 366), day of vaccination (Day 1) to Day 29, and Day 29 to study completion (Day 366).
- The absolute values and changes in hematology, chemistry, and urinalysis parameters (see section 7.1.7).
- The frequency and percentage of subjects with abnormal laboratory parameter values as classified by investigator normal ranges (low, normal, high) and as classified by

CBER toxicity grading scales, when available. **8.1.1.2 Primary Efficacy Endpoint(s)**

Not applicable.

8.1.1.3 Primary Immunogenicity Endpoint(s)

The primary immunogenicity endpoints are the GMTs measured by hSBA directed against MenC from samples collected on Day 1 (baseline, before vaccination) and Day 29 as well as the GMR of the titers (Day 29 / Day 1).

8.1.2 Secondary Endpoint(s) 8.1.2.1

Secondary Safety Endpoint(s)

Not applicable.

8.1.2.2 Secondary Efficacy Endpoint(s)

Not applicable.

8.1.2.3 Secondary Immunogenicity Endpoint(s)

The secondary immunogenicity endpoints are:

- GMTs and corresponding GMRs measured by hSBA directed against MenC for samples collected at Day 8 and Day181.
- Percentage of subjects with hSBA seroresponse at Days 8, 29, and 181. Seroresponse is defined as a post vaccination hSBA ≥8 for subjects with a baseline hSBA <4 or have an increase of at least 4 times the baseline hSBA level for subjects with prevaccination hSBA ≥4.
- Antibody geometric mean concentrations (GMCs) against MenC measured by ELISA for samples collected on Days 1 (baseline, prior to vaccination), 8, 29, and 181.
- The percentage of subjects with at least a 4-fold increase in antibody concentrations to MenC as measured by ELISA on Day 8, 29, and 181 relative to baseline (Day 1).

8.1.3 Exploratory Endpoint(s)

The exploratory endpoints are based on results of testing which may not be performed until after the study report has been finalized and will be further refined prior to testing. They include the following:

- Serum concentration of LHD153 at Day 1 baseline (prior to vaccination), Day 1 (1h , 2h, 4h, 8h, and 24h after vaccination), Day 4 by LC-MS/MS.
- Frequency of MenC polysaccharide-specific and CRM_{197}-specific B cells at Day 1 (baseline), Day 8, Day 29, and Day 181 by ELISPOT.
- Diversity of MenC polysaccharide-specific B-cell repertoire at Day 1 (baseline), Day 8, Day 29, and Day 181 by immunoglobulin cDNA sequencing.
- Functionality of antigen specific antibodies will be assessed at Day 1 (baseline), Day 8, Day 29, and Day 181 by analysis of immunoglobulin isotype, glycosylation state and their ability to fix complement, to promote antibody-dependent cell mediated cytoxicity, to induce phagocytosis and to activate FcR+ cells. If the quantity of serum available for this specific exploratory objective is limited, assessments of immunoglobulin isotype and glycosylation state will be prioritized over the other assessments.
- Frequency and quality of T cells specific for CRM_{197} at Day 1 (baseline), Day 8, and Day 29 by flow cytometry analysis using intracellular staining with a wide panel of cytokines and surface markers to identify cell populations.
- Serum concentrations of a panel of 30 chemokines and cytokines at Day 1 baseline (prior to vaccination), Day 1 (6h and 24h after vaccination), Day 4, and Day 8 by multiplex Electro-chemo-luminescence based assay.
- Gene expression profile in whole blood at Day 1 baseline (prior to vaccination), Day 1 (6h and 24h after vaccination), Day 4, and Day 8 by RNA micro array analysis.
- Number and activation status of myeloid and lymphoid cell populations at Day 1 baseline (prior to vaccination), Day 1 (24h after vaccination), Day 4 and Day 8 by flow cytometry.

8.2 Success Criteria

The study has no formal statistical hypotheses and will not be declared positive or negative according to given rules. The selection of an appropriate LHD153R adjuvant dosage for future studies will be determined by the joint evaluation of the

immunogenicity and safety profiles of each dosage group. **8.2.1 Success Criteria for Primary Objective(s)** Not applicable.

8.2.2 Success Criteria for Secondary Objective(s)

Not applicable.

8.3 Analysis Sets

8.3.1 All Enrolled Set

All screened subjects who provide informed consent and provide demographic and/or baseline screening assessments, regardless of the subject's randomization and treatment status in the study and received a Subject ID.

8.3.2 All Exposed Set

All subjects in the enrolled set who receive a study vaccination.

8.3.3 Safety Set

Safety Set (solicited adverse events and other solicited reactions)

All subjects in the Exposed Set who:

- Provide post vaccination reactogenicity data.

Safety Set (unsolicited adverse events)

All subjects in the Exposed Set who:

- Have post-vaccination unsolicited adverse event records.

Safety Set (overall)

All subjects in the Exposed Set who:

- Have either post-vaccination adverse event or reactogenicity records.

Subjects will be analyzed as "treated" (i.e., according to the vaccine a subject received, rather than the vaccine to which the subject may have been randomized).

8.3.4 Full Analysis Set (FAS) Efficacy/Immunogenicity Set

All subjects in the Enrolled Set who:

- Receive a study vaccination AND provide efficacy/immunogenicity data at relevant time points.

FAS sets will be analyzed “as randomized” (i.e., according to the vaccine a subject was designated to receive, which may be different from the vaccine the subject actually received).

8.3.5 Per Protocol (PP) Set Efficacy/Immunogenicity Set

All subjects in the FAS efficacy/immunogenicity set who:

- Are not excluded due to reasons (see section 8.3.8) defined prior to unblinding or analysis.

PPS are subsets of FAS and should always be defined even if the objectives do not require it.

Examples for subjects excluded due to other reasons than protocol deviations are:

- Subjects who withdrew informed consent.
- Premature withdrawal due to an adverse event.

Exclusions need to be considered by objective/time point, i.e., sometimes not all data of a subject but only part of the subject's data will be removed from the PPS analysis.

8.3.6 Other Analysis Sets

All subjects in the Enrolled Set who consent to additional blood draws, receive a study vaccination AND provide exploratory assay data at relevant time points will be included in an exploratory assay subset.

8.3.7 Subgroups

Selected immunogenicity analyses may be provided based on seropositivity status at baseline.

8.3.8 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. A protocol deviation may be a reason to remove data from an analysis set at the time of analysis. Reportable protocol deviations will be defined as

exclusionary from the analysis according to protocol objectives and endpoints, which will be specified in the Statistical Analysis Plan. In some cases exclusion of data may be due to a reason other than a protocol deviation, e.g. early termination.

8.4 Statistical Analysis Plan

This section provides a summary of the statistical methodology to be used. A more detailed description of analysis methods will be provided in a separate Statistical Analysis Plan which may also include additional exploratory analyses not explicitly mentioned in the following sections.

8.4.1 Analysis of Demographic and Baseline Characteristics

Descriptive statistics (number of non-missing observations, mean, standard deviation, median, minimum and maximum) for age, height and weight at enrolment will be calculated overall and by vaccine group and LHD153R adjuvant dosage.

Distributions of subjects by sex and ethnic origin will be summarized overall and by vaccine group and LHD153R adjuvant dosage.

8.4.2 Analysis of Primary Objective(s)

8.4.2.1 Analysis of Primary Safety Objective(s)

Safety of the study vaccines will be assessed in all subjects in terms of the frequency and percentage of reported AEs as well as by changes in clinical laboratory values.

8.4.2.1.1 Analysis of Extent of Exposure

The frequency and percentage of subjects with vaccinations will be summarized by vaccine group and LHD153R adjuvant dosage, by cohort and overall, for the Enrolled Set.

8.4.2.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events

All solicited adverse events will be summarized according to defined severity grading scales. Use of medication to prevent/treat fever will be summarized according to frequencies and percentages reporting “Yes” and “No”.

Frequencies and percentages of subjects experiencing each adverse event will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic adverse event overall and at each time point will also be presented.

Post-vaccination solicited adverse events reported from Day 1 to Day 14 will be summarized for the intervals Day 1-4 (without 30 minutes), Day 5-8, Day 1-8 (without 30 minutes), Day 8-14 and Day 1-14 (without 30 minutes) by maximal severity and by vaccine group and LHD153R adjuvant. The severity of solicited local adverse events, including injection-site erythema, swelling and induration will be summarized according to categories based on linear measurement: 25-50 mm, 51-100 mm, > 100 mm.

Injection site pain and systemic reactions (except fever) occurring up to Day 14 will be summarized according to “mild”, “moderate” or “severe”.

Each solicited local and systemic adverse event will also be further summarized as “none” versus “any”.

Implausible measurements (for further definition see Statistical Analysis Plan) will be left out of the analysis.

Use of antipyretics and analgesics will be summarized by frequency by type of use (prophylactic versus treatment) and percentage of subjects reporting use. The influence of antipyretics and analgesics use on the occurrence of specific adverse events (e.g., fever, pain) will be assessed.

Body temperature will be summarized by 0.5 °C and 1.0 °C increments from 36.0 °C up to ≥40 °C.

8.4.2.1.3 Analysis of Unsolicited Adverse Events

This analysis applies to all adverse events occurring during the study, judged either as probably related, possibly related, or not related to vaccination by the investigator, recorded in the CRF, with a start date on or after the date of first vaccination. AE starting prior to the first vaccination will only be listed. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class.

All reported adverse events, as well as adverse events judged by the investigator as at least possibly related to study vaccine, will be summarized according to system organ class and preferred term within system organ class. These summaries will be presented by vaccination group and LHD153R adjuvant dosage for each cohort and by interval of study observation. When an adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted.

Separate summaries will be produced for the following categories:

- Serious adverse events.
- Adverse events that are possibly or probably related to vaccine.
- Adverse events of special interest.
- New onset of chronic disease.
- Adverse event leading to withdrawal.
- Adverse events leading to a medically attended visit.
- Adverse event by data source.

Data listings of all adverse events will be provided by subject. In addition, adverse events in the categories above will be provided as listed data.

8.4.2.1.4 Analysis of Safety Laboratory Values

The investigator must review all safety laboratory results (see Section 7.1.7). Abnormal laboratory values and clinically significant changes in values from pre-vaccination (Screening Visit) will be assessed, using medical judgment, based on the FDA CBER Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" dated September 2007, or the institution's normal ranges if they differ from CBER guidance. Please see Appendix C, D and E for further details.

The following information will be provided:

- Change in absolute laboratory value from pre-vaccination (Screening Visit) and Day 1 (Visit 1) baseline to Day 1 (24 hours after vaccination), Day 8 (Visit 3) and Day 29 (Visit 6) after vaccination.
- The classification of laboratory values and/or their changes from pre-vaccination according to the CBER toxicity grading scale.
- 3 x 3 shift tables by visit using the categorization of laboratory values according to institutional normal reference ranges (below, within, above).

8.4.2.2 Analysis of Primary Efficacy Objective(s)

Not applicable.

8.4.2.3 Analysis of Primary Immunogenicity Objective(s)

8.4.2.3.1 Statistical Hypotheses

There are no statistical hypotheses associated with the primary immunogenicity objectives. All analyses are descriptive.

8.4.2.3.2 Analysis Sets

The primary immunogenicity analyses will be based on the per-protocol set (PPS) at Day 29. The primary analyses will be repeated using the Full Analysis Set (FAS) as a measure of the sensitivity/robustness of the results (further details are given in section 8.3).

8.4.2.3.3 Statistical Methods

Before any statistical analysis that assumes normally distributed observations, antibody titers will be $\log_{10}$-transformed. Individual titers below the limit of quantitation (LLQ) will be set to half that limit.

Geometric Mean Titers

The logarithmically (base 10) transformed antibody titers will be modeled using an analysis of covariance (ANCOVA) model with a qualitative factor for LHD153R adjuvant dosage (0 [for unadjuvanted MenC], 12.5, 25, 50 or 100 µg) and log (base 10) pre-vaccination titer as a covariate. The adjusted GMT and the two-sided, 95%, confidence intervals (CIs) of the GMT will be calculated based on this model as will the ratio of GMTs and corresponding CIs. The adjusted GMT and two-sided 95% CIs will be constructed by exponentiation (base 10) of the least square means of the logarithmically transformed (base 10) antibody titer. The ratio of GMTs (LHD153R adjuvant dosage minus MenC), and corresponding two-sided 95% CIs, will be constructed by exponentiation (base 10) of the least square differences obtained from this model. The model can be written as:

$$\log_{10}(y_{ik}) = \mu + \alpha_i + \beta x_{ik} + \varepsilon_{ik}$$

where μ represents a common overall mean, α_i represents the adjuvant dose group i effect, β represents the common slope for the log10 pre-vaccination titer, x_{ik} for subject k in adjuvant dose group I, and ε_{ik} represents random error for subject k in adjuvant dose group i.

Geometric Mean Ratios

The logarithmically (base 10) transformed within subject ratio of antibody titers (Day 29 / pre-vaccination) will be modeled using an analysis of variance model with a qualitative

factor for LHD153R adjuvant dosage (0 [for non-LHD153R adjuvanted MenC], 12.5, 25, 50 or 100 µg). The adjusted GMR and the two-sided, 95% CIs of the GMR will be calculated based on this model. The model can be written as:

$\log_{10}(y_{ik}) = \mu + \alpha_i + \varepsilon_{ik}$

where μ represents a common overall mean, α_i represents the adjuvant dose group i effect and ε_{ik} represents random error for subject k in adjuvant dose group i.

Handling of missing values

For immunogenicity data, it may be reasonable to consider missing immunogenicity values as missing completely at random (MCAR), i.e., not informative. Therefore, the primary analysis will comprise a complete case analysis only, without introducing any bias. Imputation methods will not be used.

8.4.3 Analysis of Secondary Objective(s) 8.4.3.1

Analysis of Secondary Safety Objective(s) Not

applicable.

8.4.3.2 Analysis of Secondary Efficacy Objective(s)

Not applicable.

8.4.3.3 Analysis of Secondary Immunogenicity Objective(s)

8.4.3.3.1 Statistical Hypotheses

There are no statistical hypotheses associated with the secondary immunogenicity objectives. All analyses are descriptive.

8.4.3.3.2 Analysis Sets

The secondary immunogenicity analyses will be based on the PPS (further details are given in section 8.3) or the appropriate subset of subjects.

8.4.3.3.3 Statistical Methods

The secondary immunogenicity endpoints are:

- GMTs and corresponding GMRs measured by hSBA directed against MenC for samples collected at Day 8 and Day181.
- Percentage of subjects with hSBA seroresponse at Days 8, 29, and 181. seroresponse is defined as a post vaccination hSBA ≥8 for subjects with a baseline hSBA <4 or have an increase of at least 4 times the baseline hSBA level for subjects with prevaccination hSBA ≥4.
- Antibody geometric mean concentrations (GMCs) against MenC measured by ELISA for samples collected on Days 1 (baseline, prior to vaccination), 8, 29, and 181.
- The percentage of subjects with at least a 4-fold increase in antibody concentrations to MenC as measured by ELISA on Day 8, 29, and 181 relative to baseline (Day 1).

The GMTs for samples collected at Day 8 and Day 181 as well as the GMCs for samples collected at Day 1, Day 8, Day 29, and Day 181 will be analyzed using the same approach as for the primary immunogenicity endpoint.

The remaining immunogenicity endpoints are based on subjects meeting criteria for seroconversion or achieving a certain threshold value. These endpoints will be summarized using frequencies and percentages by LHD153R adjuvant dosage (0 [for non-LHD153R adjuvanted MenC], 12.5, 25, 50 or 100 µg). Two-sided 95% ClopperPearson CIs will also be provided for percentages. For analyses of seroconversion, separate summaries may be provided based on seropositivity status at baseline.

8.4.4 Analysis of Exploratory Objectives

Testing and analyses of exploratory endpoints may be performed after the Clinical Study Report (CSR) has been completed, in which case these data will be submitted as an addendum to the CSR.

In general, concentration and titer results will be summarized for each LHD153R adjuvant dosage group using geometric means and associated 2-sided 95% confidence intervals; and, categorical data will be summarized using frequencies and percentages, with corresponding two-sided, 95% confidence intervals.

8.5 Sample Size and Power Considerations of Primary Objectives

Sample size is not driven by statistical assumptions for formal hypothesis testing, but was based on the safety objective for the study. The table below provides the probability for various combinations of sample size (N) and presumed true frequency of a given event within an individual vaccine group

Frequency of Event	Probability to Observe at Least 1 Subject with a Given Event For Various Choices of N			
	4	8	12	16
0.05	0.1855	0.3366	0.4596	0.5599
0.10	0.3439	0.5695	0.7176	0.8147
0.15	0.4780	0.7275	0.8577	0.9257
0.20	0.5904	0.8322	0.9313	0.9718
0.30	0.8250	0.9423	0.9862	0.9967
0.40	0.8704	0.9832	0.9978	0.9997

The proposed combinations of sample sizes within each cohort are 4 aluminium hydroxide adjuvanted MenC-CRM$_{197}$ and 16 MenC-CRM$_{197}$ plus an assigned-level of LHD153R adsorbed to aluminium hydroxide. If all four cohorts are fully enrolled, there will be 16 subjects receiving aluminium hydroxide adjuvanted MenC-CRM$_{197}$.

With 16 subjects, events which occur at a frequency of 15% or more will be detected with at least 90% probability; and, events which occur at a frequency of 10% or more will be detected with 81% probability. With 4 subjects, events which occur at a frequency of 30% or more will be detected with at least 80% probability. Intermediate values of 8 and 12 are provided to correspond to sample sizes in the MenC- CRM$_{197}$ after cohort 2 and cohort 3 are fully enrolled.

8.6 Interim Analysis

The DMC will be reviewing the accumulating safety data from the study in order to continue enrollment of subjects within a cohort and whether to enroll subjects into the next cohort.

In addition to these periodic reviews, there will be a safety and immunogenicity interim analysis for the selection of an LHD153R adjuvant dosage based on the data collected through Day 29 from subjects enrolled in all cohorts. This analysis will be performed by personnel not involved in study decisions. The results will be unblinded at the group level thereby preserving the blind for individual subjects. No adjustment to the overall alpha will be performed as the data collected subsequent to this analysis involve secondary and exploratory endpoints.

9.0 SOURCE DOCUMENTATION, STUDY MONITORING AND AUDITING

Study monitoring and auditing will be standardized and performed in accordance with the Sponsor's or delegated contract research organization's (CRO) standard operating procedures and applicable regulatory requirements (e.g., FDA, EMA, and ICH guidelines).

Prior to enrolment of the first study subject, GSK or delegate will train investigators and/or their study staff on the study protocol, all applicable study procedures, documentation practices and all electronic systems. CRFs must be completed for each enrolled subject (see section 8.3.1 for definition of enrolled subject). Documentation of screened but not enrolled subjects must be maintained at the site and made available for review by the site monitor.

9.1 Source Documentation

Prior to the start of the study, the site staff participating in the study conduct will be instructed on what documents will be required for review as source documents. The kinds of documents that will serve as source documents will be agreed between Sponsor or delegate and investigator and designees and specified in the SDA/Source Data Verification Form prior to subject enrolment.

In addition, source documentation **must** include all of the following: subject identification (on each page), eligibility and participation, proper informed consent procedures, dates of visits, adherence to protocol procedures, adequate reporting and follow-up of adverse events, documentation of prior/concomitant medication/vaccines, study vaccine receipt/dispensing/return records, study vaccine administration information, any data collected by a telephone conversation with the subject and date of completion and reason.

The subject must also allow access to the subject's medical records. Each subject must be informed of this prior to the start of the study and consent for access to medical records may be required in accordance with local regulations.

All safety data reported by subjects must be written down in source documents. If there are multiple sources of information (e.g., Subject Diary, verbal report of the subject, telephone contact details, medical chart) supporting the diagnosis of an adverse event, these sources must be identified in the source documents, discrepancies between sources clarified, the ultimate diagnosis must be justified and written in the source documents, and this diagnosis must be captured in the appropriate CRF page. The CRF must also

capture which source(s) of information were used to determine the adverse event (e.g., subject recall, medical chart, Subject Diary).

9.2 Study Monitoring, Auditing and Source Data Verification

Prior to enrolment of the first study subject, GSK or its designee (e.g., a CRO) will develop a Monitoring Plan to specify how centralized and/or on-site monitoring, including clinical specimens reconciliation, will be performed for the study. Study progress will be monitored as frequently as necessary to ensure:

- that the rights and well-being of human subjects are protected,
- the reported study data are accurate, complete, and verifiable from the source documents and
- the conduct of the study is in compliance with the current approved protocol/amendment(s), GCP and applicable regulatory requirements.

Contact details for the team involved in study monitoring will be provided to the investigator. Study data recorded on CRFs will be verified by checking the CRF entries against source documents in order to ensure data completeness and accuracy as required by study protocol.

Additional documents such as the investigator site file, pharmacy records, and informed consent documentation must also be available for review if requested. Arrangements for monitoring visits will be made in advance in accordance with the monitoring plan, except in case of emergency.

The investigator and/or site staff must make source documents of subjects enrolled in this study available for inspection at the time of each monitoring visit and Sponsor audits, when applicable. These documents must also be available for inspection, verification and copying, as required by regulations, by officials of the regulatory health authorities (e.g., FDA, EMA and others) and/or ECs/IRBs. The investigator and study site staff must comply with applicable privacy, data protection and medical confidentiality laws for use and disclosure of information related to the study and enrolled subjects.

10.0 DATA MANAGEMENT

10.1 Data Entry and Management

In this study, all clinical data (including, but not limited to, AE/SAEs, concomitant medications, medical history, and physical assessments), safety data, and immunogenicity data will be entered into an EDC system, which is compliant with Title 21 Part 11

policies of the Code of Federal Regulations (FDA, 1997). The data system includes password protection and internal quality checks. The EDC system will be designed and validated by the Sponsor prior to activation for data entry by sites. The investigator or designated delegate must review data entered and electronically sign the CRFs to verify their accuracy.

Access to the EDC system for data entry or review will require training and distinct individual access code assignments to those site staff members who will be entering study data and those involved in study oversight who may review study data. Data are collected within the EDC system, to which the Sponsor and site monitors have exclusively "read only" access.

Paper CRFs will be provided for each pregnant subject by the Sponsor. All appropriate pregnant subject data collected will be recorded on this form. One copy must be retained by the investigator, and all other copies (including the original copy) will be returned as directed by the Sponsor. Instructions on how to complete this form will be provided to the investigator.

10.2 Data Clarification

As part of the conduct of the trial, the Sponsor may have questions about the data entered by the site, referred to as queries. The monitors and the Sponsor are the only parties that can generate a query. All corrections and clarifications will be entered into the EDC system and will be identified by the person entering the information, the reason for the change, as well as the time of the changes made. If changes are made to a previously and electronically signed CRF, the investigator must confirm and endorse the changes

10.3 Data Protection

GSK respects the subjects' rights to privacy and will ensure the confidentiality of their medical information in accordance with all applicable laws and regulations.

The Sponsor as Data Controller according to the European Directive on the protection of individuals with regard to the processing of personal data and on the free movement of such data (95/46/EC) confirms herewith compliance to Directive 95/46/EC in all stages of Data Management.

11.0 RECORD RETENTION

Investigators must retain all study records required by GSK and by the applicable regulations in a secure and safe facility. The investigator must consult a GSK representative before disposal of any study records, and must notify the Sponsor of any change in the location, disposition, or custody of the study files. Essential documents must be retained for 15 years. “Essential documents” are defined as documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. These documents should be retained for a longer period, however, if required by the applicable national regulatory or institutional requirements.

These principles of record retention will also be applied to the storage of laboratory samples, provided that the integrity of the stored sample permits testing.

12.0 USE OF INFORMATION AND PUBLICATION

GSK assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov, and in compliance with current regulations.

GSK also assures that key results of this clinical study will be posted in a publicly accessible database within the required time-frame from the End of Study as defined in section 3.9.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

GSK must be notified of any intent to publish data collected from the study and prior approval from GSK must be obtained prior to submission for publication.

13.0 ETHICS

13.1 Regulatory and Ethical Compliance

The study will be conducted in compliance with the protocol, GCP and applicable regulatory requirement(s).

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, European Directive 2001/20/EC, GSK codes on protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki (European Council 2001, US Code of Federal Regulations, ICH 1997).

13.2 Informed Consent Procedures

Eligible subjects may only be included in the study after providing written informed consent or assent, as described in section 5.1.1. Before the start of the study, the investigator will have the informed consent and any other materials that will be provided to the subjects reviewed and approved by the IRB/EC. This review and approval will be documented and stored with other study documents. The investigator or designee must fully inform the subject or legal guardian of all pertinent aspects of the study. A copy of the written informed consent will be given to the subject or the designee. The subject/designee must be allowed ample time to ask about the details of the study and to make a decision as to whether or not to participate in the study. The subject and/or legal guardian(s) **must** sign the consent form indicating their agreement to participate in the study before any study-related procedures are conducted. The informed consent process may be conducted up to 28 days prior to vaccination on Day 1. If the subject is unable to read and write, a witness must be present during the informed consent discussion and at the time of informed consent signature.

Prior to the start of the study, GSK will provide to investigators a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by GSK before submission to the IRB/EC and a copy of the approved version must be provided to GSK after IRB/EC approval.

Women of childbearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements indicated in the protocol for the duration of the study. In case of doubt on

the ability of a subject to adhere to these requirements, that subject should not be allowed in the study

13.3 Responsibilities of the Investigator and IRB/EC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB/EC before study start. Properly constituted IRB/EC is defined in ICH Guideline for Good Clinical Practice E6 (R1), Section 3 (ICH, 1997). A signed and dated statement that the protocol and informed consent have been approved by the IRB/EC must be given to GSK before study initiation. Prior to study start and at any time the protocol is amended during study conduct, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to GSK monitors, auditors, GSK Clinical Quality Assurance representatives, designated agents of GSK, IRBs/ECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform GSK immediately that this request has been made.

The investigator also responsible for the following:

- Maintaining a list of appropriately qualified persons to whom the investigator has delegated significant study-related duties.
- Demonstrating the capability of recruiting the required number of suitable subjects within the recruitment period.
- Demonstrating sufficient time and staffing to properly conduct and complete the study within the agreed study period.
- Ensuring that all persons assisting with the study are adequately informed about the protocol, the investigational product(s), and their study-related duties and functions
- Ensuring that appropriately trained health care professionals are responsible for all study-related medical decisions and for ensuring appropriate medical care of subjects experiencing any adverse event related to the study.
- If permission to do so is given by the subject, ensuring that the subject's primary healthcare provider is informed of the subject's participation in the study.

The investigator should not implement any deviation from, or changes of the protocol without agreement by the Sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone

number(s)). In addition, the investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to study subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

(a) to the IRB/IEC for review and approval/favourable opinion,

(b) to the Sponsor for agreement and, if required,

(c) to the regulatory authority(ies).

13.4 Protocol Amendments

An amendment is a written description of change(s) to or formal clarification of a study protocol which may impact on the conduct of the clinical study, potential benefit of the clinical study, or may affect subject safety, including changes of study objectives, study design, subject population, sample sizes, study procedures, or significant administrative aspects. An administrative change of a study protocol is a minor correction or clarification that has no significant impact on the way the clinical study is to be conducted and no effect on subject safety (e.g., change of telephone number(s), logistical changes). Protocol amendments must be approved by GSK, health authorities where required, and the IRB/EC. In cases when the amendment is required in order to protect the subject safety, the amendment can be implemented prior to IRB/EC approval. Notwithstanding, the need for formal approval of a protocol amendment, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, GSK should be notified of this action, the IRB/EC at the study site, and, if required by local regulations, the relevant health authority should be informed within 10 working days.

14.0 REFERENCE LIST

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APPENDIX A: GRADING SCALES FOR SOLICITED LOCAL ADVERSE EVENTS*

(Adapted from CBER 2007b)

Adverse event Following Administration of Injectable Product	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Pain	present but does not interfere with activity	interferes with activity	prevents daily activity
Induration / Swelling / Erythema	25 – 50 mm	51 – 100 mm	> 100 mm

*This toxicity grading scale is adapted from CBER 2007 to enable ease of reporting by Subjects in the source documents for 'patient reported' solicited adverse events.. 'Grade 4' is not listed here but will be defined in the Statistical Analysis Plan as necessary.

APPENDIX B: GRADING SCALES FOR SOLICITED SYSTEMIC ADVERSE EVENTS*

(Adapted from CBER 2007b)

Systemic Adverse event		Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Fever	**°C**	38.0 – 38.4	38.5 – 38.9	39.0 – 40
	°F	100.4 – 101.1	101.2 - 102	102.1 - 104
Chills		present but does not interfere with activity	interferes with activity	prevents daily activity
Loss of Appetite		Loss of appetite without decreased oral intake	decreased oral intake without weight loss	decreased oral intake with weight loss
Nausea		Nausea present but not interfering with oral intake	Nausea leading to decreased oral intake	Nausea leading to minimal to no oral intake
Vomiting		1-2 episodes/24 hours	>2 episodes/24 hours	requires outpatient hydratation
Diarrhea		2-3 loose stools /24 hours	4-5 loose stools /24 hours	6 or more watery stools /24 hours or requires outpatient IV hydration
Generalized Myalgia		present but does not interfere with activity	interferes with activity	prevents daily activity
Generalized Arthralgia		present but does not interfere with activity	interferes with activity	prevents daily activity
Headache		present but does not interfere with activity	interferes with activity	prevents daily activity
Fatigue		present but does not interfere with activity	interferes with activity	prevents daily activity
Generalized Rash		localized area of the skin (1 extremity only)	moderate area of the skin (2 or more body regions without whole body involvement)	most of the skin
Urticaria		localized area of the skin (1 extremity only)	moderate area of the skin (2 or more body regions without whole body involvement)	most of the skin

*This toxicity grading scale is adapted from CBER 2007b to enable ease of reporting by Subjects in the source documents for 'patient reported' solicited adverse events. 'Grade 4' is not listed here but will be defined in the statistical analysis plan as necessary

APPENDIX C: TOXICITY SCALES FOR LABORATORY ABNORMALITIES (SERUM CLINICAL CHEMISTRY)

Serum*,**	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)*****
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN

*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

**Laboratory values that fall in the normal range may be assigned a category of "Grade 0."

***The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value. "ULN" = the upper limit of the normal range.

APPENDIX D: TOXICITY SCALES FOR LABORATORY ABNORMALITIES (HEMATOLOGY)

Hematology*,**	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0

Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Platelets Decreased cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000

*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
**Laboratory values that fall in the normal range may be assigned a category of "Grade 0."

APPENDIX E: TOXICITY SCALES FOR LABORATORY ABNORMALITIES (URINE)

Urine*,**	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
**Laboratory values that fall in the normal range may be assigned a category of "Grade 0."

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Document Approval Certificate /

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The individuals listed have approved this document for implementation using an electronic signature in the

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UserName:) Title: Cluster Physician Date: Wednesday, 24 June 2015, 12:14 GMT
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CLINICAL STUDY PROTOCOL SPONSOR SIGNATURE PAGE

Study Number: V132_01EXP

Protocol Title: A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine in Healthy Adults (18-45 years of age)

Date of Final Issued Protocol and Version: 18 Jun 15, Version 4

Signature page for sponsor's representative

The following sponsor's representative has reviewed and approved the protocol entitled "A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine in Healthy Adults (18-45 years of age)." In addition, this study protocol has been approved by the GSK Protocol Review Committee and received an electronic approval signature on 18 Jun 15.

[redacted] 26/JUN/15

Cluster Physician, GSK Date, DD MMM YY

[redacted]

Printed Name of Cluster Physician, GSK

PPD

CLINICAL STUDY PROTOCOL AMENDMENT

Study Number: V132_01EXP

Protocol Title: A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine in Healthy Adults (18-45 years of age)

Amendment Number 4

Revised Protocol version 5.0 issued on 11 SEP 2015

The present amendment reflects changes to the Protocol version 4.0 issued on 18JUN15

DESCRIPTION OF CHANGE(S) AND RATIONALE:

CHANGE	LOCATION(S) OF CHANGE	RATIONALE FOR CHANGE
Deletion of assessment of functional antibody response from the exploratory objectives and endpoints	Synopsis (Pages 10, 14 and 17) Section 2.3 'Exploratory Objectives' (Page 29) Section 7.4 'Exploratory measurements' (Pages 73 and 74) Section 8.1.3 'Exploratory Endpoints' (Page 76)	The highly-specialized collaborator that was anticipated for this exploratory endpoint expressed it could no longer commit to the study deliverables for logistic reasons.

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Atlas EDMS. PPD

UserName: PPD Title: Cluster Physician Date: Monday, 14 September 2015, 09:30 GMT
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CLINICAL STUDY PROTOCOL V132_01EXP Version 5

A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine in Healthy Adults (18-45 years of age)

EUDRACT No. 2014-002430-31

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PROTOCOL SYNOPSIS V132_01EXP

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
GlaxoSmithKline Biologicals S.A.	V132_01EXP	MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and Meningococcal C-CRM$_{197}$ Conjugate Vaccine
Title of Study: A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine in Healthy Adults (18-45 years of age)		
Study Period: Approximately 12 months for each subject		**Clinical Phase:** Phase 1

Background and Rationale:

Neisseria meningitidis (*N. meningitides*)serogroup C (MenC) is one of the major serogroups causing invasive meningococcocal disease. Case fatality in Germany has ranged between 6% and 8% between 1999 and 2006, and has remained generally consistent across the different European countries, varying between 6-11%, with the case fatality rate being notably higher for serogroup C disease than for serogroup B. The safety and immunogenicity of the GSK Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) has been confirmed through years of commercial use. For children over the age of 12 months, for adolescents and for adults a single dose is recommended. For infants between 2 and 12 months of age, the recommended schedule for primary immunization with the Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) is two doses given with an interval of at least 2 months A more potent Meningococcal CCRM$_{197}$ Conjugate Vaccine formulation might enable a reduction of the antigen dosage and/or a reduction in the number of doses needed in infants. One approach to achieve more potent well-characterized sub-unit vaccines - like the Meningococcal C-CRM$_{197}$ Conjugate Vaccine - is the use of new adjuvants that activate the Toll-like receptor (TLR) pathway.

GSK is developing a small molecule immune potentiator (SMIP) LHD153 that is an agonist for TLR7. The objective driving the development of LHD153 is to achieve a vaccine adjuvant with strong immunopotentiating properties and minimal side effects. In line with this objective, it has been postulated that the ideal SMIP should remain local

and target innate immune cells at the injection site. To this end, LHD153 contains a functional phosphonate group to allow for adsorption to aluminium hydroxide. The

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
GlaxoSmithKline Biologicals S.A.	V132_01EXP	MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and Meningococcal C-CRM$_{197}$ Conjugate Vaccine

arginine salt derivative of this compound is LHD153R. Preclinical results from animal models for bacterial and viral antigens, including MenC, MenB, rabies, HIV and respiratory syncytial virus (RSV) showed increased functional antibodies and antigenspecific T-cells with LHD153R adsorbed to aluminium hydroxide (Aluminium Hydroxide/LHD153R) when compared to aluminium hydroxide adjuvanted controls. *In vitro* toxicity screens confirmed that LHD153R is not phototoxic, genotoxic or mutagenic. Furthermore, toxicology studies in dog and rats showed that intramuscular (IM) injection of Aluminium Hydroxide/LHD153R was well tolerated. Importantly, in contrast to free LHD153R, toxicokinetic analysis in rats and dogs confirmed very limited exposure of LHD153 when LHD153R was adsorbed to aluminium hydroxide after IM injection.

The aim of this Phase 1 clinical study is to assess the safety of Aluminium Hydroxide/LHD153R adjuvanted MenC-CRM_{197} conjugate vaccine (MenCCRM$_{197}$/Aluminium Hydroxide/LHD153R) and to compare the antibody-mediated immune response elicited by MenC-CRM_{197}/Aluminium Hydroxide/LHD153R with the licensed aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (Menjugate®). Furthermore, a comprehensive set of exploratory objectives has been selected to assess the systemic exposure of LHD153 after intramuscular injection of MenC-CRM_{197}/Aluminium Hydroxide/LHD153R, to evaluate the quality of the specific immune response against MenC-CRM_{197} in detail and to evaluate biomarkers that may be predictive of safety and/or innate immune activation.

The licensed Meningococcal C-CRM_{197} Conjugate Vaccine (Menjugate®) has been selected as the primary vaccine candidate to assess the safety and immunopotentiating properties of Aluminium Hydroxide/LHD153R for several reasons. Firstly, the safety and immunogenicity profiles of the Meningococcal C-CRM_{197} Conjugate Vaccine (Menjugate®) have been well established through years of commercial use. Secondly, a more potent MenC-CRM_{197} conjugate vaccine might enable a reduction of the antigen dosage or the number of doses needed in infants. Finally, MenC-CRM_{197} is a wellcharacterized, single conjugate antigen preparation which provides an ideal setting to evaluate the potential of this new Aluminium Hydroxide/LHD153R adjuvant.

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Study Objectives:

Primary Safety Objective:

To assess the safety of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R as compared to that of aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine.

Primary Immunogenicity Objective:

To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine at Day 29, as measured by human complement serum bactericidal assay (hSBA) directed against MenC.

Secondary Immunogenicity Objectives:

1. To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal CCRM$_{197}$ Conjugate Vaccine, at Day 8 and Day 181 after vaccination, as measured by hSBA directed against MenC. Baseline antibody titers will also be measured by hSBA.
2. To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal CCRM$_{197}$ Conjugate Vaccine at Day 8, Day 29 and Day 181 after vaccination, as measured by an enzyme-linked immunosorbent assay (ELISA) to MenC. Baseline antibody concentrations will also be measured by ELISA.

Exploratory Objectives:

1. To evaluate the systemic exposure of LHD153 at several early time-points after IM injection of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R or aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine.
2. To explore the frequency of B cells specific for MenC polysaccharide and CRM$_{197}$ protein at baseline (Day 1) and at Day 8, Day 29 and Day 181 after vaccination with

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MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R or the aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine. Subsequently, the B cell repertoire of the antigen specific B cells will be analyzed in a selected subset of subjects.

3. To explore the baseline T cell mediated immunity to CRM$_{197}$ and to evaluate the frequency and quality of CRM$_{197}$ specific T cells induced by MenC-CRM$_{197}$/Aluminium Hydroxide/ LHD153R compared to aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine at Day 8 and Day 29.
4. To evaluate biomarkers that may be predictive for safety and/or innate immune activation.

Study Design:

This Phase 1, randomized, observer-blind, dosage-escalation study will be performed at a single center. In total, approximately 80 healthy male and healthy non-pregnant female adults (18-45 years of age) will be enrolled in the study. Subjects will be randomized to receive a single IM vaccination of either the licensed aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine (i.e. 10 µg MenC conjugated to CRM$_{197}$, adjuvanted with 1 mg aluminium hydroxide) or one of four dosages of the investigational vaccine, MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R (i.e. 10 µg MenC conjugated to CRM$_{197}$, adjuvanted with 1 mg aluminium hydroxide and one of four dosages [12.5, 25, 50 or 100 µg] of LHD153R).

For the dosage-escalation of LHD153R, the subjects will be enrolled into 1 of 4 cohorts, in a stepwise manner with 20 subjects per cohort. Subjects in all cohorts will be randomized in a 1:4 ratio, to receive either aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine (control) or MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R with increasing doses of LHD153R.Cohort 1 will receive 12.5 µg of LHD153R; Cohort 2 will receive 25 µg of LHD153R; Cohort 3 will receive 50 µg of LHD 153; and Cohort 4 will receive 100 µg of LHD153R (Table 1).

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Table 1: Subjects Randomized per Cohort and Treatment Dosage Group

Cohort	Group	Subjects/ Group	MenC Dosage* (µg)	Adjuvant Dosages		Total Volume/Dose	Total Subjects/Cohort
				Aluminium Hydroxide (mg)	LHD153R (µg)		
1	A	4	10	1	0	0.5 mL	20
	B	16	10	1	12.5	0.5 mL	
2	A	4	10	1	0	0.5 mL	20
	C	16	10	1	25	0.5 mL	
3	A	4	10	1	0	0.5 mL	20
	D	16	10	1	50	0.5 mL	
4	A	4	10	1	0	0.5 mL	20
	E	16	10	1	100	0.5 mL	

*Conjugated to 12.5-25 µg CRM_{197}

After vaccination, all subjects will be confined to the clinical site for 24 hours for clinical observation, including but not limited to observations for solicited and unsolicited adverse events, body temperature measurements and blood sampling for exploratory endpoint measurements.

Importantly, all cohorts will have a staggered entry based on Data Monitoring Committee (DMC) reviews.

- For each cohort, the first 5 subjects (i.e. the first 1:4 randomization block) to receive either aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (n=1) or MenC-CRM_{197}/Aluminium Hydroxide/LHD153R (n=4) will be treated at a vaccination rate of 1 subject each day.
- After entry of the first 5 subjects in each cohort, the enrollment will be paused. The remaining 15 subjects for each cohort will be enrolled only after DMC review of the safety results obtained through Day 14 has been finalized (Table 2).
- In addition, enrollment of the first 5 subjects in the next cohort will only proceed after the Day 14 safety results of the first 5 subjects of the previous cohort have been reviewed by the DMC (Table 2).
- Furthermore, all available Day 14 and Day 29 safety results will be included in DMC reviews between the different enrollment stages.

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Table 2: Overview of staggered entry of subjects based on DMC reviews

Stage	Dosage Cohort	MenC-CRM$_{197}$/ Aluminium Hydroxide (n)	MenC-CRM$_{197}$/ Aluminium Hydroxide /LHD153R (n)
1	1	1	4
Enrollment pause until DMC review of Stage 1 Day 14 Safety Results			
2	1	3	12
	2	1	4
Enrollment pause until DMC review of Stage 1 Day 29 and Stage 2 Day 14 Safety Results			
3	2	3	12
	3	1	4
Enrollment pause until DMC review of Stage 2 Day 29 and Stage 3 Day 14 Safety Results			
4	3	3	12
	4	1	4
Enrollment pause until DMC review of Stage 3 Day 29 and Stage 4 Day 14 Safety Results			
5	4	3	12

The DMC review will be performed according to predefined stopping/pausing guidelines used to ensure the safety of study subjects. These stopping/pausing guidelines are based on FDA guidance and with grading scales from the CBER Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials". See protocol section 3.6 for further details.

Safety Measurements

Schedule of safety data collection:

- Solicited local and systemic adverse events (AEs), body temperature and all unsolicited AEs will be collected until Day 14.
- All serious adverse events (SAEs), medically attended AEs, AEs leading to study withdrawal, new onset of chronic disease (NOCDs), and adverse events of special interest (AESIs) will be collected from the date of signed informed consent to study completion at Day 366.
- All concomitant medications administered in relation to the reported AEs will be

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collected from vaccination to study completion at Day 366.

Solicited local AEs include injection site erythema, injection site induration, injection site pain and injection site swelling. Solicited systemic AEs include body temperature ≥ 38.0°C (as measured orally), loss of appetite, nausea, fatigue, generalized myalgia, generalized arthralgia, headache, chills, vomiting, diarrhea, generalized rash and urticaria.

All AESIs will be reported in the same manner as SAEs. All AEs will be monitored until resolution or, if the AE becomes chronic, a cause is identified. If an AE is unresolved at the conclusion of the study, a clinical assessment will be made by the investigator and the medical monitor to determine whether or not continued follow-up of the AE is warranted.

The relationship of the study treatment to any AE will be determined by the investigator as probably related, possibly related, or not related; the relationship of the study treatment to any SAE will be determined by the investigator as probably related/suspected, or not related.

Safety Laboratory Parameters

To assess laboratory AEs, blood and urine samples will be collected from each subject as outlined in Table 3 to perform blood chemistry, hematology, and urine analyses.

Safety laboratory samples will be drawn from all subjects at pre-vaccination screening (between Day -28 and Day -3) at Day 1 (pre-vaccination and 24h after vaccination), at Day 8 and at Day 29. Safety laboratory assessments will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, liver function tests (ALT, AST), a complete blood count and C-reactive protein. A urine sample will be collected at the same time-points and will be assessed for the presence of protein, glucose and red blood cells.

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Primary and Secondary Immunogenicity Measurements

Four blood samples per subject (i.e. at Day 1, Day 8, Day 29 and Day 181) will be collected for serum preparation and determination of antibody-mediated immune responses to MenC-CRM$_{197}$ as outlined in Table 3 and Table 4. See section 7.3 for further details.

Exploratory Measurements

In all subjects who agree by signing a separate Informed Consent, additional blood samples will be collected at Day 1, Day 4, Day 8, Day 29 and Day 181 for exploratory assays as outlined in Table 3 and Table 4. The purpose of these assays is to assess the systemic exposure of LHD153, to determine the frequency and quality of B- and T-cells specific for MenC polysaccharide and/or CRM$_{197}$ and to evaluate biomarkers that may be predictive of safety and/or innate immune activation. Subsequently, MenC-CRM$_{197}$ specific B-cell repertoires will be analyzed in a selected subset of subjects, dependent on the results from primary and secondary immunogenicity measurements and the volume of blood remaining for additional testing. See section 7.4 for further details. All exploratory analyses may be performed after the Clinical Study Report (CSR) has been completed, in which case these data will be submitted as an addendum to the CSR.

Number of Subjects planned:

Approximately 80 adult subjects will be randomized, with anticipated dropout rates of 5% by Day 181 (last serology time point), and 10%, by Day 366 (last safety time point).

Sample size is not driven by statistical assumptions for formal hypothesis testing, but the proposed number of subjects will be sufficient to provide a descriptive summary of the safety and immunogenicity of the study vaccine.

Study Population and Subject Characteristics:

Healthy adult male and female volunteers between 18-45 years of age, inclusive.

The list of inclusion and exclusion criteria is included in protocol section 4.0.

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Study Vaccines:

The MenC-CRM$_{197}$ conjugate is a lyophilized powder consisting of 10 µg of MenC polysaccharide conjugated to 12.5-25 µg CRM$_{197}$ carrier protein. The MenC-CRM$_{197}$ lyophilized powder will be reconstituted with adjuvant by the unblinded designated site staff member who is to follow the procedure as described in the vaccine preparation instructions in the Investigator Site File (i.e. the vaccine will be prepared in the clinic prior to administration).

The lyophilized MenC-CRM$_{197}$ powder will be reconstituted with either:

(a) aluminium hydroxide adjuvant

(b) Aluminium Hydroxide/LHD153R adjuvant with specified dosages of LHD153R (12.5, 25, 50 or 100 µg)

The components for each formulation of MenC-CRM$_{197}$ will be provided in a separate kit.

Aluminium Hydroxide/LHD153R with specified dosages of LHD153R will be prepared by dilution of the highest Aluminium Hydroxide/LHD153R dosage (100 µg of LHD153R) with aluminium hydroxide.

In each cohort, subjects will be randomized to receive one injection of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R adjuvant or aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine. The 0.5 mL of vaccine will be injected IM in the deltoid muscle, with preference that the injection is administered in the nondominant arm.

Primary Safety Endpoint:

Safety will be assessed by measuring the frequency of local and systemic solicited AEs, unsolicited AEs, SAEs, AESIs, NOCDs, and safety laboratory data for all subjects. Specifically,

- The frequency and percentage of subjects with solicited local and systemic AEs through Day 14. Time intervals after vaccination that will be summarized are: 30

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min post-vaccination, Days 1-4 (without 30 min), Days 5-8, Days 8-14, Days 1-8 (without 30 min) and Days 1-14 (without 30 min).

- The frequency and percentage of subjects with any unsolicited AEs from the day of vaccination (Day 1) to Day 14.
- The frequency and percentage of subjects with SAEs, medically attended AEs, AEs leading to study withdrawal, NOCDs, AESIs for the following time periods: day of signed informed consent until study completion (Day 366), day of vaccination (Day 1) to Day 29 and Day 29 to study completion (Day 366).
- The absolute values and changes in hematology, chemistry, and urinalysis parameters.
- The frequency and percentage of subjects with abnormal laboratory parameter values as classified by investigator normal ranges (low, normal, high) and as classified by CBER toxicity grading scales, when available.

Primary Immunogenicity Endpoint:

Geometric mean titers (GMTs) measured by hSBA directed against MenC from samples collected on Day 1 (baseline, before vaccination) and Day 29 as well as the GMR of the titers (Day 29 / Day 1).

Secondary Immunogenicity Endpoints:

- GMTs and corresponding GMRs measured by hSBA directed against MenC for samples collected at Day 8 and Day181.
- Percentage of subjects with hSBA seroresponse at Day 8, Day 29, and Day 181. seroresponse is defined as a post vaccination hSBA $\geq$8 for subjects with a baseline hSBA <4 or have an increase of at least 4 times the baseline hSBA level for subjects with pre-vaccination hSBA $\geq$4.
- Antibody geometric mean concentrations (GMCs) against MenC measured by ELISA for samples collected on Day 1 (baseline, prior to vaccination), Day 8, Day 29, and Day 181.
- The percentage of subjects with at least a 4-fold increase in antibody concentrations

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to MenC measured by ELISA on Day 8, Day 29, and Day 181 relative to baseline (Day 1).

Exploratory Endpoints:

Testing and analyses of exploratory endpoints may be performed after the Clinical Study Report (CSR) has been completed, in which case these data will be submitted as an addendum to the CSR.

1. Serum concentration of LHD153 at Day 1 baseline (prior to vaccination), Day 1 (1h , 2h, 4h, 8h, and 24h after vaccination) and Day 4 by LC-MS/MS.
2. Frequency of MenC polysaccharide-specific and CRM$_{197}$-specific B cells at Day 1 (baseline), Day 8, Day 29, and Day 181 by ELISPOT.
3. Diversity of the MenC polysaccharide-specific B-cell repertoire at Day 1 (baseline), Day 8, Day 29, and Day 181 by immunoglobulin cDNA sequencing.
4. Frequency and quality of T cells specific for CRM$_{197}$ at Day 1 (baseline), Day 8, and Day 29 by flow cytometry using intracellular staining with a panel of cytokines and staining of surface markers to identify cell populations.
5. Serum concentrations of a panel of 30 chemokines and cytokines at Day 1 baseline (prior to vaccination), Day 1 (6h and 24h after vaccination), Day 4, and Day 8 by electrochemo-luminescence based assay.
6. Gene expression profile in whole blood at Day 1 baseline (prior to vaccination), Day 1 (6h and 24h after vaccination), Day 4, and Day 8 by RNA micro array analysis.
7. Number and activation status of myeloid and lymphoid cell populations at Day 1 baseline (prior to vaccination), Day 1 (24h after vaccination), Day 4 and Day 8 by flow cytometry.

Statistical Analyses:

The study is exploratory in nature, thus analyses will be descriptive and no formal hypothesis testing will be performed.

Primary Safety Analyses

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The primary safety analyses will be based on the safety set for solicited and unsolicited adverse events. There is no statistical null hypothesis associated with the safety objective, which will be analyzed descriptively.

Immunogenicity Analyses

The primary immunogenicity analyses will be based on the per-protocol set (PPS) on Day 29. The primary analyses will also be performed using the Full Analysis Set (FAS) as a measure of the sensitivity/robustness of the results. All other immunogenicity assessments will be performed using the PPS or the appropriate subset of subjects. The antibody concentrations/titers will be summarized using GMC/GMTs and two-sided 95% confidence intervals (CIs) constructed by exponentiation (base 10) of the least square means of the logarithmically transformed (base 10) antibody titer. The 95% CIs will be obtained from an analysis of covariance (ANCOVA) with baseline concentration/titer as a covariate. Additional details will be further described in the Statistical Analysis Plan.

The immunogenicity endpoints based on subjects meeting criteria for seroconversion or achieving a certain threshold value will be summarized using frequencies and percentages and associated two-sided 95% Clopper-Pearson CIs. For analyses of seroconversion, separate summaries may be provided based on seropositivity status at baseline.

Interim Analysis: An Interim Analysis will be performed on the immunogenicity and safety data collected from all subjects until Day 29, after all cohorts have been enrolled. Further details regarding the interim analysis are contained in section 8.6.
Data Monitoring Committee: A DMC will be implemented to review safety data during scheduled periodic reviews. The DMC will review safety data collected until Day 14, as described in the DMC charter and in the Statistical Analysis Plan, after enrollment of the first 5 subjects in each cohort, before proceeding with enrollment of the remaining 15 subjects in each cohort.

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In addition, enrollment of the first 5 subjects of the next cohort will only proceed after the Day 14 safety results of the first 5 subjects of the previous cohort have been reviewed. Furthermore, all available Day 14 and Day 29 safety results will be included in DMC reviews between the different enrollment stages. Further information regarding the DMC is discussed in more detail in the protocol, section 3.7.		

Table 3: Time and Events Table – Treatment Period (until Day 29)

	Visit Type	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit	Phone Call	Clinic Visit
	Study Day	-28 to -3	1	4	8	15	22	29
	Visit Window (Days)	n/a	n/a	n/a	-1/+1	+1	n/a	-2/+2
	Visit Number	Screening	1	2	3	4	5	6
Study Event	**References**							
Study Treatment								
Vaccination	Section 5.2		X					
Screening and Safety								
Informed Consent	Section 5.1.1	X						
Demographic Data & Medical History	Sections 5.1.2	X						
Physical Exam	Sections 5.1.2 and 5.2.1	X	X[a]					
Safety Laboratory blood draw (10 ml)	Section 7.1.7	X	X[b]		X			X
Urinalysis	Sections 7.1.7	X	X[b]		X			X
Pregnancy Test	Sections 5.1.2 and 5.2.1	X	X[a]					
Exclusion/Inclusion Criteria	Section 4.0	X	X[a]					
Randomization	Section 5.2.3		X[a]					
30 min and 24 hr Post Injection Assessment	Section 5.2.5		X[c]					
Subject Diary Dispensed with Training	Section 5.2.5		X					
Subject Diary Reminder	Section 5.2.5			X	X			

Subject Diary Reviewed and Collected	Section 5.3.1					X		
Assess all solicited AEs	Section 7.1.1 and 7.1.3					X		
Assess all unsolicited AEs	Sections 7.1.2 and 7.1.3	X	X	X	X	X		

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	Visit Type	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Phone Call**	**Clinic Visit**
	Study Day	**-28 to -3**	**1**	**4**	**8**	**15**	**22**	**29**
	Visit Window (Days)	**n/a**	**n/a**	**n/a**	**-1/+1**	**+1**	**n/a**	**-2/+2**
	Visit Number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**
Study Event	**References**							
Assess SAEs	Section 7.1.4	X	X	X	X	X	X	X
Assess AESIs	Section 7.1.4.1	X	X	X	X	X	X	X
Assess NOCDs, medically attended AEs, AEs leading to withdrawal	Sections 7.1.3	X	X	X	X	X	X	X
Assess relevant medications	Sections 5.1.2 and 6.5	X	X	X	X	X	X	X
Blood draws for Immunogenicity and Exploratory Objectives								
Serum Blood Draws (Primary/Secondary Objectives; 10 mL)	Section 3.5		X_a		X			X
Serum Blood Draws (Exploratory Objectives; 5 mL)	Section 3.5		X_d	X	X			
Whole Blood Draws (Exploratory Objectives; 3 mL)	Section 3.5		X_e	X				
Whole Blood Draws (Exploratory Objectives; 5 mL)	Section 3.5		X_f	X	X			
Whole Blood Draws (Exploratory Objectives; 20 mL)	Section 3.5		X_g	X				
Whole Blood Draws (Exploratory Objectives; 50 mL)	Section 3.5							X

Whole Blood Draws (Exploratory Objectives; 70 mL)	Section 3.5		X_a		X			

Notes: ɔn.

a. Procedure must be performed prior to vaccination.
b. Two blood draws (2 x 10 ml) and two urine samples must be taken at Study Day 1, i.e. at baseline (prior to vaccination) and at 24h after vaccinati
c. Body temperature measurement must be performed at 30 min, 2, 4, 6, 8, 10, 12, 18 and 24h after vaccination.
d. Three Serum Blood Draws (3 x 5ml) must be taken at Study Day 1, i.e. at baseline (prior to vaccination), at 6h and at 24h after vaccination.
e. Six Whole Blood Draws (6 x 3 mL) must be taken at Study Day 1, i.e. at baseline (prior to vaccination) and at 1, 2, 4, 8 and 24h after vaccination.
f. Three Whole Blood Draws (3 x 5 mL) must be taken at Study Day 1, i.e. at baseline (prior to vaccination), at 6h and at 24h after vaccination.
g. Whole Blood Draw (20 mL) at Study Day 1 must be taken at 24h after vaccination.

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Table 4: Time and Events Table – Follow-up Period (until Day 366)

	Visit Type	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Phone Call**	**Phone Call**	**Clinic Visit**
	Study Day	**85**	**113**	**181**	**209**	**271**	**366**
	Visit Window (Days)	**-7 to +7**	**-7 to +7**	**-7 to +7**	**-14 to +14**	**-14 to +14**	**-14 to +14**
	Visit Number	**7**	**8**	**9**	**10**	**11**	**12**
Study Event	**References**						
Safety							
Assess SAEs	Section 7.1.4	X	X	X	X	X	X
Assess AESI	Section 7.1.4.1	X	X	X	X	X	X
Assess NOCDs, medically attended AEs, AEs leading to withdrawal	Sections 7.1.3	X	X	X	X	X	X
Assess relevant medications	Sections 5.1.2 and 6.5	X	X	X	X	X	X
Blood draws for Immunogenicity and Exploratory Objectives							

Serum Blood Draw (Secondary Objective; 10 mL)	Section 3.5			X			
Whole Blood Draw (Exploratory Objectives; 50 mL)	Section 3.5			X			
Study Completion Procedures							
Study Termination[a]	Section 5.5						X

Notes:
a. Subjects who terminate the study early are recommended to complete certain study-related procedures. See section 5.5 for further details.

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LIST OF ABBREVIATIONS

ADCC	Antibody-dependent cell mediated cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BZN	Benzonaphthyridines
CBER	Center for Biologics Evaluation and Research
cDNA	Complementary deoxyribonucleic acid
CI	Confidence interval
CRF	Case report form
CRM_{197}	Cross Reacting Material 197
CSR	Clinical Study Report
DMC	Data Monitoring Committee
EC	Ethics committee
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
ELISPOT	Enzyme-Linked ImmunoSpot
EMA	European Medicines Agency
FACS	Fluorescence-activated cell sorting
FAS	Full analysis set
FDA	Federal Drug Agency
GCP	Good clinical practice
GMC	Geometric mean concentration
GMP	Good manufacturing practice

GMT	Geometric mean titer
GMR	Geometric mean ratio
HEENT	Head, ears, eyes, nose and throat
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
hSBA	Human complement serum bactericidal assay
ICF	Informed consent form
ICH	International Committee for Harmonization
IM	Intramuscular
IRB	Institutional review board
IV	Intravenous
LLQ	Lower limit of quantification
MenC	Meningococcal type C
MPL	Monophosphoryl lipid A
NCR	No carbon required
NOCD	New Onset of Chronic Disease
PEG	Polyethylene glycol
PO	Per oral
PP	Per protocol
RNA	Ribonucleic acid (RNA
SAE	Serious Adverse Event
SMIP	Small molecule immune potentiator
TLR	Toll-like receptor
VSAE	Vaccine serious adverse event

1.0 BACKGROUND AND RATIONALE

1.1 Background

MenC-CRM$_{197}$ Conjugate Vaccine

Meningococcal disease worldwide is predominantly a disease of infants and young children. *N. meningitidis* serogroup B and C remain the most prevalent strains in North America and Europe, (Rosenstein, N. et al., 2001) and together cause more than 95% of reported cases of meningococcal disease in Europe (Connolly, M, et al., 1999). In Europe, *N. meningitidis* serogroup C (MenC) is one of the major serogroups causing invasive disease. Case fatality in Germany has ranged between 6% and 8% between 1999 and 2006, and has remained generally consistent across the different European countries, varying between 6-11%, with the case fatality rate being notably higher for serogroup C disease than for serogroup B (European Centre for Disease Prevention and Control, 2011). Since MenC vaccination was added to Germany's routine schedule for children in 2006, there has been a reported decline in MenC incidence. However, the decline was not as rapid when compared to other European countries (Hellenbrand, W. et al., 2013).

The GSK Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) comprises MenC oligosaccharides conjugated to the protein carrier, CRM$_{197}$, a nontoxic mutant of diphtheria toxin. The vaccine has been shown to be safe and immunogenic and able to prime infants, toddlers and young children for immunological memory (see Meningococcal C-CRM$_{197}$ Conjugate Vaccine Summary of Product Characteristics).

In Germany, the Standing Committee on Vaccination (STIKO) of the Robert Koch Institute recommends a single dose of MenC conjugate vaccine in children over the age of 12 months as part of the routine vaccination campaign (Robert Koch Institute Epidemiologisches Bulletin, August 2013). For specific indications, e.g. in case of postexposure prophylaxis, the recommended schedule for primary immunization of infants between 2 to 12 months of age with a MenC conjugate vaccine is two dosages given with an interval of at least 2 months.

Although the Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) represents an example of how vaccination with a well characterized, purified polysaccharide antigen can yield pivotal public health triumphs, there remains a need for further improvement of the MenC vaccine. A more potent MenC vaccine formulation might yield an increase in the magnitude of the antigen-specific immune response enabling a reduction of the antigen dosage. Furthermore, induction of a more rapid antigen-specific immune response may enable a reduction in the number of doses needed for post-exposure prophylaxis in infants.

Vaccine Adjuvants

Immunization with purified protein or polysaccharide antigens typically results in the induction of a modest antibody response with little or no T cell response when compared to vaccines comprised of whole or killed bacteria or viruses that have inherent immunepotentiating activity. The need to increase the immunogenic response of wellcharacterized and purified antigens that display suboptimal immunogenicity when used alone affirms the essential role for the use of adjuvants. Vaccine adjuvants may significantly reduce the amount of antigen needed (Del Giudice, G, et al., 2013) and may induce a more rapid immune response enabling a reduction in the number of doses in a regimen.

Besides reducing the antigen dosage or number of doses in the vaccine regimen, there is now an increased appreciation of the capacity of adjuvants to increase not just overall antibody titer but also to increase the number of functional antibodies and/or antibodies with higher affinity for vaccine antigens. Many pathogens, such as influenza viruses, HIV, human papilloma virus (HPV) and the malaria parasite, display substantial antigenic drift, subtype and/or strain variations. Therefore, the ability of adjuvants to broaden an immune response profile could be crucial to the success of vaccines against such targets. Previous studies have shown that the broadening effect of adjuvants may be mediated via expansion of B cell diversity, not merely through increased titers (Khurana, et al., 2010, 2011). Clinically, antibody response broadening by adjuvants such as AS04 or oil-inwater emulsions has been demonstrated in HPV vaccines and influenza, respectively (Bissett, SL et al., 2014; Del Giudice, G et al., 2013).

One unmet need is the development of vaccines for effective T cell responses. Several vaccines in development are aimed at eliciting T cell responses, which historically have not been induced by the most commonly used adjuvants in vaccines for human use, such as aluminium hydroxide. Therefore, an objective of many adjuvant discovery and development programs is to elicit more effective engagement of T-helper cells for optimizing the quality, breadth and durability of antibody responses, or, to induce effector CD4+ or CD8+ T cells to kill intracellular pathogens. One approach for new generation vaccines is the use of agonists for Toll-like receptors (TLRs) that activate innate immune receptors, mainly on antigen presenting cells, and facilitate the generation of T helper cell responses.

Adjuvants that are currently employed in human vaccines licensed for use in the USA and/or Europe include aluminium salts, oil-in-water emulsions (MF59, AS03 and AF03), virosomes, and AS04 (Alving, CR, et al., 2012). Among the most advanced adjuvants systems is AS04 which is used in the Cervarix® HPV vaccine and consist of the TLR4 ligand monophosphoryl lipid A (MPL) combined with aluminium salt. MPL, along with

QS21, is also part of the adjuvant system (AS01) in the RTS, S malaria vaccine which has been evaluated in a Phase 3 clinical trial (Regules, JA, et al., 2011). Another clinically advanced adjuvant is CpG oligodeoxynucleotide (ODN), a TLR9 ligand contained in the Heplisav® vaccine candidate for hepatitis B from Dynavax, that has completed a Phase 3 clinical trial (Reed, SG, et al., 2013).

Small molecule immune potentiators as a new class of vaccine adjuvants

A new class of adjuvants, small molecule immune potentiators (SMIPs), has been identified that activate immune cells by targeting TLR7 and TLR8. Imiquimod and Resiquimod (R848) are clinically advanced TLR7 and/or TLR8 SMIPs that are used as immunotherapeutics. Although Imiquimod and Resiquimod have been studied extensively as vaccine adjuvants in preclinical models (Vasilakos et al. 2013), they were never optimized for this use and, in general, compare poorly to other pre-clinical and clinical adjuvant candidates. Furthermore, when Imiquimod is applied topically (it is a licensed topical treatment for viral and malignant skin lesions) it induces strong local and systemic inflammatory reactions, and is poorly tolerated (Bauza, et al. 2009; Campanelli, et al. 2005; Meyer, et al. 2008).

Unlike traditional drugs, TLR7 SMIPs activate innate immunity and initiate a cascade of immune responses that can have systemic impact and endure after the compound has been cleared from the organism. For SMIPs as vaccine adjuvants this difference is highlighted further by the fact that 2-3 local IM injections drive antigen-specific B and T cell responses at distal sites and these can provide protection in the form of immunologic memory (Tacken, et al. 2011; Ilyinskii, et al., 2014). Therefore, limiting the systemic exposure of the SMIP adjuvants has been postulated as an approach to both increase vaccine efficacy and minimize side effects associated with systemic and generalized inflammation. GSK is currently developing a novel adjuvant, containing a SMIP from the benzonaphthryridines (BZN) series, LHD153, which targets TLR7. The objective driving the discovery of this new TLR7 ligand was to develop a vaccine adjuvant with high efficacy in increasing the vaccine specific immune response and with minimal side effects. To obtain this objective it was postulated that the ideal compound would remain localized at the site of injection to help trigger the immune reaction to vaccine antigens, yet maintain a low systemic distribution. At the same time this compound had to be soluble to make industrial scale-up and manufacturing feasible. Soluble BZN were engineered so that they could be formulated with aluminium salts with the aim of limiting their systemic exposure and keeping them localized in the muscle for short time after immunization. The strongest adsorption to aluminium hydroxide particles is obtained through ligand exchange of hydroxyl and/or phosphate groups on the surface of aluminium hydroxide or phosphate with soft anionic moieties such as phosphates, phosphonates, phosphites, sulfates and carboxylates. To drive the adsorption to

aluminium hydroxide through ligand exchange, LHD153 was functionalized with a polyethylene glycol (PEG) linker and a terminal phosphonate. Furthermore, LHD153 was stabilized with arginine salt to allow scale up for GMP manufacturing, yielding LHD153R. As predicted, unformulated LHD153R exhibited high levels of systemic exposure when injected IM in mice, rats and dogs, whereas the serum concentrations of LHD153R adsorbed to aluminium hydroxide (Aluminium Hydroxide/LHD153R) was dramatically reduced. Moreover, Aluminium Hydroxide/LHD153R remained localized to the injection site.

Preclinical studies using Aluminium Hydroxide/LHD153R to date confirm the activation of the TLR7 pathway and subsequent boost of both the humoral and cellular immune response. Moreover, Aluminium Hydroxide/LHD153R displays a unique pharmacokinetic profile as demonstrated by its minimal systemic exposure, potentially minimizing any systemic inflammatory response associated with tolerability issues. Aluminium hydroxide/LHD153R has achieved proof of concept in animal models using several vaccine antigens including MenC, MenB, rabies, HIV and respiratory syncytial virus (RSV). In vitro toxicity of LDH153R has been assessed, and in vivo nonclinical tolerability and safety of LHD153R and Aluminium Hydroxide/LHD153R have been evaluated in rats, dogs and non-human primates. LHD153R was not phototoxic, genotoxic or mutagenic (Ames and chromosomal aberration tests), and did not cause local or systemic toxicity in dogs or rats. Furthermore, Aluminium Hydroxide/LHD153R was well tolerated in rhesus monkeys.

1.2 Rationale

The aim of this study is to assess the safety of Aluminium Hydroxide/LHD153R adjuvanted MenC-CRM$_{197}$ conjugate vaccine (MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R) and to compare the antibody-mediated immune response elicited by MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R with the licensed aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®).

Furthermore, a comprehensive set of exploratory objectives has been selected to assess the systemic exposure of LHD153 after intramuscular injection and to evaluate the quality of the specific immune response against MenC-CRM$_{197}$ in detail and to evaluate biomarkers that may be predictive of safety and/or innate immune activation.

The licensed Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) has been chosen as the primary vaccine candidate to assess the safety and immunopotentiating properties of Aluminium Hydroxide/LHD153R for several reasons. Firstly, the safety and immunogenicity profiles of the Meningococcal C-CRM$_{197}$ Conjugate Vaccine have been well established through years of commercial use. Secondly, a more potent

Meningococcal C-CRM$_{197}$ Conjugate Vaccine might enable a reduction of the antigen dosage or the number of doses needed in infants between 2 and 12 months of age. Finally, Meningococcal C-CRM$_{197}$ is a well-characterized, single conjugate antigen preparation which provides an ideal setting to explore the potential of this new Aluminium Hydroxide/LHD153R adjuvant.

2.0 OBJECTIVES

2.1 Primary Objectives

Primary Safety Objective

To assess the safety of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R as compared to that of aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine.

Primary Immunogenicity Objective

To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine at Day 29, as measured by human complement serum bactericidal assay (hSBA) directed against MenC.

2.2 Secondary Objectives

Secondary Immunogenicity Objective(s)

1. To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal CCRM$_{197}$ Conjugate Vaccine at Day 8 and Day 181 after vaccination, as measured by hSBA directed against MenC. Baseline antibody titers will also be measured by hSBA.
2. To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal CCRM$_{197}$ Conjugate Vaccine, at Day 8, Day 29 and Day 181 after vaccination, as measured by an enzyme-linked immunosorbent assay (ELISA) to MenC. Baseline antibody concentrations will also be measured by ELISA.

2.3 Exploratory Objectives

1. To evaluate the systemic exposure of LHD153 at several early time-points after IM injection of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R or Meningococcal CCRM$_{197}$ Conjugate Vaccine.
2. To explore the frequency of B cells specific for MenC polysaccharide and CRM$_{197}$ protein at baseline (Day 1) and at Day 8, Day 29 and Day 181 after vaccination with MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R or the aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine. Subsequently, the B cell repertoire of the antigen specific B cells will be analyzed in a selected subset of subjects.
3. To explore the baseline T cell mediated immunity to CRM$_{197}$ and to evaluate the frequency and quality of CRM$_{197}$ specific T cells induced by MenCCRM$_{197}$/Aluminium Hydroxide/ LHD153R compared to aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine at Day 8 and Day 29.
4. To evaluate biomarkers that may be predictive for safety and/or innate immune activation.

3.0 STUDY DESIGN

3.1 Overview of Study Design

This is a Phase 1, randomized, observer blind, adjuvant dosage-escalation study. It will be performed at a single center. In total, approximately 80 healthy male and healthy nonpregnant female adults (18-45 years of age) will be enrolled in the study.

Subjects will be randomized to receive a single IM vaccination of either the licensed aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (Menjugate®) or the investigational vaccine, MenC-CRM_{197}/Aluminium Hydroxide/LHD153R.

The dosage of LHD153R will be escalated from 12.5 µg to 100 µg. For the dosageescalation of LHD153R, the subjects will be enrolled into 1 of 4 cohorts, in a stepwise manner with 20 subjects per cohort. Subjects in all cohorts will be randomized in a 1:4 ratio, to receive either aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (control) or MenC-CRM_{197}/Aluminium Hydroxide/LHD153R with increasing doses of LHD153R. Subjects assigned to MenC-CRM_{197}/Aluminium Hydroxide/LHD153R in Cohort 1 will receive 12.5 µg of LHD153R; Subjects in Cohort 2 will receive 25 µg of LHD153R; Subjects in Cohort 3 will receive 50 µg of LHD153R; Subjects in Cohort 4 will receive 100 µg of LHD153R (Table 3.1-1).

Table 3.1-1: Subjects Randomized per Cohort and Treatment Dosage Group

Cohort	Group	Subjects/ Group	MenC Dosage* (µg)	Adjuvant Dosages		Total Volume/Dose	Total Subjects/Cohort
				Aluminium Hydroxide (mg)	LHD153R (µg)		
1	A	4	10	1	0	0.5 mL	20
	B	16	10	1	12.5	0.5 mL	
2	A	4	10	1	0	0.5 mL	20
	C	16	10	1	25	0.5 mL	
3	A	4	10	1	0	0.5 mL	20
	D	16	10	1	50	0.5 mL	
4	A	4	10	1	0	0.5 mL	20
	E	16	10	1	100	0.5 mL	

*Conjugated to 12.5-25 µg CRM_{197}

All cohorts will have a staggered entry. For each cohort, the first 5 subjects (i.e. the first 1:4 randomization block) to receive either aluminium hydroxide adjuvanted

Meningococcal C-CRM$_{197}$ Conjugate Vaccine (n=1) or MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R (n=4) will be vaccinated at rate of 1 subject each day.

After entry of the first 5 subjects in each cohort, the enrollment will be paused. The remaining 15 subjects for each cohort will be enrolled only after DMC review of the safety results obtained through Day 14 has been finalized (Table 3.1-2). In addition, enrollment of the first 5 subjects of the next cohort will only proceed after the Day 14 safety results of the first 5 subjects of the previous cohort have been reviewed by the DMC. Furthermore, all available Day 14 and Day 29 safety results will be included in DMC review between the different enrollment stages.

Table 3.1-2: Overview of staggered entry of subjects based on DMC reviews

Stage	Dosage Cohort	MenC-CRM$_{197}$/ Aluminium Hydroxide (n)	MenC-CRM$_{197}$/ Aluminium Hydroxide /LHD153R (n)
1	1	1	4
Enrollment pause until DMC review of Stage 1 Day 14 Safety Results			
2	1	3	12
	2	1	4
Enrollment pause until DMC review of Stage 1 Day 29 and Stage 2 Day 14 Safety Results			
3	2	3	12
	3	1	4
Enrollment pause until DMC review of Stage 2 Day 29 and Stage 3 Day 14 Safety Results			
4	3	3	12
	4	1	4
Enrollment pause until DMC review of Stage 3 Day 29 and Stage 4 Day 14 Safety Results			
5	4	3	12

Post-vaccination procedures include collection of urine specimens at Day 1, Day 8 and Day 29 for safety assessment and blood specimens at Day 1, Day 8, Day 29 and Day 181 for safety assessment and evaluation of the primary and secondary immunogenicity endpoints. Furthermore, additional blood specimens will be collected for assessment of exploratory endpoints at Day 1, Day 4, Day 8, Day 29 and Day 181 from those subjects that signed an additional informed consent concerning blood collection for exploratory assessment.

3.2 Study Period

Each subject should expect to participate in the study for approximately 12 months, from the time of enrolment through the last study visit.

3.3 Blinding Procedures

This study is designed as an observer-blind study. For each dosage cohort, subjects, investigators, laboratories and the sponsor will be blinded to vaccine assignments.

To maintain the blindness within each cohort, designated nurse(s) or physician(s) will be responsible for administering the study vaccines to the subjects, and will be instructed not to reveal the identity of the study vaccines neither to the subject nor to the investigative site personnel (investigator, study nurse, monitor) involved in the conduct or monitoring of the trial. This (these) designated individual(s) will have no contact with the subjects after the administration of the study vaccine. Furthermore, unblinded monitors are assigned to reconcile actual vaccine treatment.

Study unblinding, at the group level, is planned for an Interim Analysis of the safety and immunogenicity data obtained up to Day 29 after all cohorts are enrolled and for full unblinding at the End of Study.

Except in the case of medical necessity, a subject's treatment should not be unblinded without the approval of the Sponsor. In such instance of medical emergency, every effort should be made to contact the Sponsor prior to unblinding. If unblinding should occur (by either accidental unblinding or emergency unblinding for a serious adverse event) prior to completion of the study, the investigator must promptly contact the Sponsor and document the circumstances on the appropriate forms. Instructions regarding emergency unblinding will be provided to the investigator.

3.4 Data Collection

3.4.1 Data Collected from Subjects

The following data will be collected from each subject over the duration of their study participation:

- Demographic Information
- Adverse Events
- Medical History
- Concomitant Medications
- Vital signs

All data collected must only be identified using the Subject ID, as described in section 5.2.3.

3.4.2 Tools Used for Data Collection

Data will be recorded in the Subject Diary and collected on Case Report Forms (CRFs).

Subject Diary

Subject Diaries will be the only source document allowed for solicited local and systemic adverse events (including body temperature measurements), starting after the initial 24 hours post-vaccination observation period at the clinic. The following additional rules apply to documentation of safety information collected in the Subject Diary:

1. No corrections or additions to the Subject Diary will be allowed after it is delivered to the site.
2. Any blank or illegible fields on the Subject Diary must be described as missing in the CRF.
3. Any corrections to the Subject Diary must be performed by the person completing the Subject Diary and should include a single strike through line through the incorrect value or text with a brief explanation for each change, the initials of that person, and date of correction.

Case Report Forms

This study utilizes CRFs to collect study-related data from each subject. A qualified site staff member(s) is required to enter subject data in the CRFs based on the medical information available in each subject's record. The following additional rules apply to documentation of Subject Diary information collected in the CRFs:

1. The site must enter all readable entries in the Subject Diary into the CRF, including those values that may be biologically implausible (e.g. body temperature: 400°C).
2. Any illegible or implausible data should be reviewed with the subject. If an underlying solicited or unsolicited adverse event is described on review with the subject, this should be described in the source document and reported as an unsolicited adverse event in the appropriate CRF (e.g., if the subject above confirms body temperature of 40°C on the day in which body temperature: 400°C was written into his/her Subject Diary, this fever of 40°C should be recorded in the appropriate CRF).

3. Any newly described safety information (including a solicited adverse event) must not be written into the Subject Diary and must be described in the study file as a verbally reported adverse event. Any adverse event reported in this fashion must be described as an unsolicited adverse event and therefore, entered in the appropriate CRF.

Data should be entered into the CRF in a timely fashion following each subject's clinic visit, study procedure, or phone call. Each subject's CRF casebook will be compared with the subject's source records by a GSK-approved study monitor (or designee) over the duration of the study in order to ensure data collection accuracy.

3.5 Collection of Clinical Specimens

The following clinical specimens are required to be collected from each subject in this study:

- Blood
- Urine

Processing of each specimen should be completed by a qualified site member. Testing of clinical specimens will be performed by a GSK or designated laboratory.

Blood Specimens

Before Vaccination

- At the Pre-vaccination Screening Visit (between Day -28 to -3) one sample of approximately 10 ml blood will be drawn from all subjects.
- At Visit 1 (Day 1) - prior to vaccination – two samples of approximately 10 ml blood will be drawn from all subjects.
- At Visit 1 (Day 1) - prior to vaccination - the following blood samples will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays:
  - One sample of approximately 3 ml
  - Two samples of approximately 5 ml
  - One sample of approximately 70 ml

After Vaccination

- At Visit 1 (Day 1) - 1 hour after vaccination - one sample of approximately 3 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 2 hours after vaccination - one sample of approximately 3 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 4 hours after vaccination - one sample of approximately 3 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 6 hours after vaccination – two samples of approximately 5 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 8 hours after vaccination - one sample of approximately 3 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 24 hours after vaccination - one sample of approximately 10 ml blood will be drawn from all subjects.
- At Visit 1 (Day 1) - 24 hours after vaccination - the following blood samples will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays:
  - One sample of approximately 3 ml
  - Two samples of approximately 5 ml
  - One sample of approximately 20 ml
- At Visit 2 (Day 4) the following blood samples will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays:
  - One sample of approximately 3 ml
  - Two samples of approximately 5 ml
  - One sample of approximately 20 ml
- At Visit 3 (Day 8) two samples of approximately 10 ml blood will be drawn from all subjects.

- At Visit 3 (Day 8) the following blood samples will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays
  - Two samples of approximately 5 ml
  - One sample of approximately 70 ml
- At Visit 6 (Day 29) two samples of approximately 10 ml blood will be drawn from all subjects.
- At Visit 6 (Day 29) one sample of approximately 50 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 9 (Day 181) one sample of approximately 10 ml blood will be drawn from all subjects.
- At Visit 9 (Day 181) one sample of approximately 50 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.

The blood will be used for screening and safety laboratory assessments, immunological serology assays, pharmacokinetic analysis, cell mediated immunity assays and gene expression and protein production assays. See section 5.1.2, section 5.2.1 and section 7.0 for additional details.

Processing of each blood specimen should be completed in accordance with the study specific Clinical Specimen Laboratory Manual.

The total amount of blood collected over the study period for all subjects will be approximately 90 ml.

For subjects that signed an additional informed consent for blood collection for exploratory assays the total amount of blood collected over the study period will be approximately 441 ml.

Urine Specimens

Urine will be collected at the Pre-vaccination Screening Visit (between Day -28- to -3), at Visit 1 (Day 1; before vaccination and 24 hours after vaccination), at Visit 3 (Day 8) and at Visit 6 (Day 29). Results will be recorded in the source document and CRF.

Urine will be collected from all subjects for safety laboratory assessments and drugs-ofabuse testing. Furthermore, urine will be collected for pregnancy testing in all females.

3.6 Stopping/Pausing Guidelines

Stopping/pausing guidelines are predefined criteria that halt the conduct of a study (either a vaccine group or the entire study). These guidelines are used to ensure the safety of study subjects.

The following criteria, based on FDA guidance and with grading scales adapted from the CBER Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive vaccine Clinical Trials", will be used for this study:

1. The study will be halted (no new enrollments and no further investigational product administered until a full safety review by the DMC and consultation with the IRB/EC and the health authorities is completed) if one of the following occurs
   a. One subject experiences a serious adverse event (SAE) assessed as possibly or probably related to investigational product or,
   b. There is a subject death assessed as possibly or probably related to the investigational product.
2. If one or more subjects experience a Grade 4 AE (see Appendix C, D, and E), vital sign or clinically significant laboratory abnormality that cannot be clearly attributed to another cause, vaccination will be suspended until a full safety review by the DMC is performed.
3. If six or more subjects experience a Grade 3 AE (see Appendix A, B, C, D, and E), vital sign or clinically significant laboratory abnormality, dosage escalation will be suspended for that vaccine until a full safety review by the DMC is performed.

The sponsor or the investigator (following consultation with the sponsor) has the right to discontinue the study at any time. If the clinical study is prematurely terminated, the investigator must promptly inform the study subjects and must assure appropriate therapy and follow-up for the subjects. All procedures and requirements pertaining to the archiving of the documents must be followed. All other study materials (such as study vaccines) must be returned to the sponsor or destroyed after sponsor approval.

3.7 Data Monitoring Committee

A DMC will be formed to review safety data during scheduled periodic reviews. The

DMC may also perform reviews on an ad hoc basis as needed. DMC membership will consist of at least 3 individuals who are external to the site and sponsor, and will include 1 statistician who is independent from the study team.

Subjects will be enrolled in a stepwise manner in each of the four vaccine dosage cohorts (Cohort 1: 12.5 µg LHD153R, Cohort 2: 25 µg of LHD153R, Cohort 3: 50 µg of LHD153R and Cohort 4: 100 µg of LHD153R). The DMC will review all safety data, as described in the DMC charter and in the Statistical Analysis Plan, after the first 5 subjects in each cohort have completed Visit 4 and their data are available for analysis, and before enrollment of the remaining subjects in the respective cohort and before enrollment of the first 5 subjects in the subsequent cohort. In addition, in between the different enrollment stages, the DMC will review all available safety data of subjects that have completed Visit 4 and all available safety data of subjects that have completed Visit 6.

The specific roles and responsibilities of the DMC members and other personnel involved will be documented in the DMC charter. The DMC charter will be finalized before the start of the study and will outline in detail all pausing and stopping rules according to the Clinical Study Protocol.

3.8 Premature Withdrawal from Study

Subjects may withdraw at any time, or be dropped from the study at the discretion of the investigator should any untoward effects occur and/or for safety reasons. In addition, a subject may be withdrawn by the investigator or the Sponsor if he/she violates the study plan or for administrative reasons. The investigator or study coordinator must notify the Sponsor immediately when a subject has been withdrawn due to an adverse event.

The circumstances above are referred to as premature withdrawal from the study, and the reason for premature withdrawal should be clearly documented and detailed in the source documentation. The investigator should make every attempt to evaluate the subject's safety, including resolution of ongoing AEs, at the time of premature withdrawal. If a subject wants to withdraw from the study prior to the last planned study visit, the subject will be asked to be followed for safety for the duration of the study. When a subject withdraws, or is withdrawn, from the study, the procedures described in section 5.5.1 should be completed if possible.

The reasons for premature withdrawal from the study include: Adverse event, death, withdrawal of consent, lost to follow-up, administrative reason, and protocol deviation. These reasons are described in greater detail below.

Adverse Event

For any subject withdrawn from study participation prior to the planned Study Termination Visit, it is important to determine if an AE was associated with the reason for discontinuing the study. This AE must be identified on the appropriate CRF page by indicating "Withdrawn from study due to AE". Any ongoing AEs at the time of study withdrawal must be followed until resolution or stabilization.

Death

For any subject withdrawn from study participation due to death, this should be noted on the appropriate CRF page and the associated SAE that led to the death must be reported.

Withdrawal of consent

The subject can withdraw consent for participation in the study at any time without penalty or loss of benefit to which the subject is otherwise entitled. Reason for early termination should be deemed as "withdrawal of consent" if the subject withdraws from participation due to a non-medical reason (i.e., reason other than AE). If the subject intends to withdraw consent from the study, the investigator should clarify if the subject will withdraw completely from the study or if the subject will continue study participation for safety, or a subset of other study procedures. If the subject requests complete withdrawal from the study, no further study interventions will be performed with the subject.

Lost to Follow-Up

For subjects who fail to show up for study visits (clinic or telephone contacts), study staff is encouraged to make at least three documented attempts to contact the subject by telephone and at least one documented written attempt to contact the subject to encourage the completion of study termination procedures. These efforts to contact the subject must be recorded in the source document. The termination date for the subject to be captured on the appropriate CRF page is the date of the last contact (clinic visit or telephone) with the subject.

Administrative Reason

Examples for subjects withdrawn from the study due to administrative reason can include: Sponsor decision to terminate the study, subject meeting a pre-specified withdrawal criterion, subject discontinuation for insurance issues, moving, no time, etc. This reason should be noted in the appropriate CRF page and any ongoing AEs at the time of study withdrawal must be followed until resolution/stabilization.

If the clinical study is prematurely terminated by the Sponsor, the investigator is to promptly inform the study subjects and local EC/IRB and should assure appropriate therapy and follow up for the subjects. All procedures and requirements pertaining to the archiving of study documents should be followed. All other study materials (study medication/vaccines, etc.) must be returned to the Sponsor.

For subjects who are withdrawn from the study due to receipt of an excluded medication/vaccination or due to significant protocol non-compliance, this reason should be noted in the appropriate CRF page.

Protocol Deviation

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. In general, subjects associated with protocol deviations may remain in the study unless continuation in the study jeopardizes the subject's health, safety, or rights.

Investigators will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact GSK or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a change to the protocol would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by GSK and approved by the IRB/EC and health authorities it cannot be implemented.

Any subject who becomes pregnant during the study should be encouraged to continue participating in the study for safety follow-up. The site must complete a Pregnancy Report CRF (initial report) as soon as possible after learning of pregnancy occurrence (see section 7.1.6 for further details). If the subject withdraws from the study for any of the above categories except death, the site will obtain permission from the subject to continue to remain in contact with her until the outcome of the pregnancy is known, even if the outcome is not known until after the subject reaches the end of the routine study period.

3.9 End of Study

Most clinical trials intended to support the efficacy/immunogenicity and safety of an Investigational Product proceed to full completion of planned sample size accrual.

A subject is considered to have completed this study when he/she has: (1) received the intended dose of study vaccine and (2) completed 365 days (Visit 12) of safety follow-up after receiving the study vaccine.

Evaluation of the primary and secondary immunogenicity objectives requires the testing of biological samples from all study subjects, which can only be completed after all samples are collected. The last samples for the analysis of the primary and/or secondary objectives will be taken at Visit 9 (Day 181). For the purpose of this protocol, End of Study is defined as the completion of the testing of such biological samples, to be achieved no later than 8 months after collection of the last biological sample at Visit 9.

4.0 SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

In order to participate in this study, all subjects must meet all of the inclusion criteria described.

1. Male or female individuals of 18 through 45 years of age on the day of informed consent.
2. Healthy volunteers with good physical and mental health status, determined on the basis of the medical history, a physical examination and the results of the screening tests as judged by the investigator.
3. Individuals who have voluntarily given written informed consent after the nature of the study has been explained according to local regulatory requirements, prior to study entry.
4. Individuals who can comply with study procedures including follow-up[1].
5. Individuals that are able to understand, read and write German language.
6. Females of childbearing potential who are using an effective birth control method[2] which they intend to use for at least 30 days after the study vaccination.

4.2 Exclusion Criteria

Each subject must not have or must not be:

1. Progressive, unstable or uncontrolled clinical conditions.
2. Hypersensitivity, including allergy, to any component of vaccines, medicinal products or medical equipment whose use is foreseen in this study.

[1] A subject is considered to be compliant if the Investigator judges that the subject will complete the Subject Diary, return for all the follow-up visits and be available for telephone calls as scheduled in the study.

[2] The following birth control methods are considered effective:

- Hormonal contraceptive (such as oral, injection, transdermal patch, implant) if used for at least 30 days prior to informed consent
- Diaphragm with spermicide, tubal occlusion device
- Intrauterine device (IUD)
- Tubal ligation
- Male partner using condom with spermicide
- Male partner having been vasectomized at least six months prior to informed consent

3. Clinical conditions representing a contraindication to intramuscular vaccination and blood draws.
4. Abnormal function of the immune system resulting from:
   a. Clinical conditions.
   b. Systemic administration of corticosteroids (PO/IV/IM) for more than 14 consecutive days within 90 days prior to informed consent.
   c. Administration of antineoplastic and prescription immunomodulating agents or radiotherapy within 90 days prior to informed consent.
5. Received immunoglobulins or any blood products within 180 days prior to informed consent.
6. Received an investigational or non-registered medicinal product within 30 days prior to informed consent or intend to participate in another clinical study at any time during the conduct of this study.
7. Vulnerable subjects (e.g. persons kept in detention), study personnel or an immediate family or household member of study personnel, subjects with legal incapacity or limited legal capacity
8. Any relevant deviation from the laboratory parameters at screening as judged by the investigator.
9. Previously received any vaccine that included a MenC antigen.
10. Previously suspected or confirmed disease caused by *N. meningitides.*
11. Had household contact with and/or intimate exposure to an individual with culture proven MenC.

12. A positive serum or urine pregnancy test prior to the study vaccine administration or are currently lactating.

13. A positive drugs-of-abuse test prior to the study vaccine administration

14. Received any other vaccines within 30 days prior to enrolment in this study or who are planning to receive any vaccine within 30 days from the administration of study vaccines.

15. Any other condition that, in the opinion of the investigator, might interfere with the results of the study or pose additional risk to the subject due to participation in the study.

4.3 Criteria for Delay of Vaccination or Blood Draw

There may be instances when individuals meet all eligibility criteria for vaccination or blood draw yet have a transient clinical circumstance which may warrant delay of vaccination or blood draw. Under such circumstances, a subject may be considered eligible for study enrolment after the appropriate window for delay has passed and inclusion/exclusion criteria have been rechecked, and if the subject is confirmed to be eligible.

Reasons for delay of vaccination include:

- Body temperature elevation ≥38.0°C (measured orally) within 3 days prior to intended study vaccination.
- Use of antipyretics and/or analgesic medications within 24 hours prior to vaccination.

Reasons for delay of blood draw include:

- Subject has received a dose of systemic antibiotics less than 6 days before blood collection for the hSBA directed against MenC.

5.0 STUDY PROCEDURES

The sections that follow provide an overview of the procedures that are to be followed in enrolling, evaluating, and following subjects who participate in this clinical study. Visits can be either clinic visits or safety follow-up telephone calls, as specified in the Table below and in the Time and Events Tables 3 and 4 of the Study Synopsis.

Table 5.0-1: Study procedures

Visit Category	Procedures
Pre-vaccination Clinic Visit	Section 5.1 describes procedures to be followed prior to subject enrollment, including: informed consent and screening procedures.
Vaccination Clinic Visit	Section 5.2 describes procedures to be followed during the vaccination clinic visit, including: prevaccination procedures, enrolment, randomization, vaccination and post-vaccination procedures.
Post-vaccination Visits	Section 5.3 describes follow-up clinic visits and safety follow-up calls.
Unscheduled Visits	Section 5.4 describes possible procedures to be followed at unscheduled clinic visit.
Study Termination Visit	Section 5.5 describes procedures to be followed at the last study visit for a subject (may include early termination visit).

5.1 Pre-vaccination Clinic Visit(s)

The Pre-vaccination Clinic Visit must be performed in the period between Day -28 and Day -3.

This section describes the procedures that must be performed for each potential subject prior to enrollment, including obtaining informed consent and screening.

5.1.1 Informed Consent

"Informed consent" is the voluntary agreement of an individual or his/her legal guardian(s) to participate in research. Consent must be given with free will of choice, and without undue inducement. The individual must have sufficient knowledge and understanding of the nature of the proposed research, the anticipated risks and potential benefits, and the requirements of the research to be able to make an informed decision.

Informed consent following local IRB/EC guidance **must** be obtained before conducting any study-specific procedure (i.e., all of the procedures described in the protocol). Prior to any additional blood sample collection for exploratory objectives, a secondary informed consent **must** be signed by subjects. The process of obtaining informed consent should be documented in the subject source document in addition to maintaining a copy of the signed and dated informed consent.

5.1.2 Screening

After an individual has consented to participate in the study and informed consent is signed, that individual will be given a unique Screening Number. The subject's unique Screening Number will be documented in the Screening and Enrolment log. The eligibility of the subject will be determined based on the inclusion and exclusion criteria listed in section 4.0 and evaluated during this screening procedure.

Screening procedures at the Pre-vaccination Clinical Visit (between Day -28 and Day -3) will include the following:

- Review of demographic data, including age, gender, race, body weight and height.
- Review of medical history, including but not limited to any medical history, ongoing illnesses or injuries that may be relevant to subject eligibility for study participation. Relevant medical history can also include any medical history that contributes to the understanding of an adverse event that occurs during study participation, if it represents an exacerbation of an underlying disease/pre-existing problem.
- Perform physical examination, including but not limited to:
  - Assessment of general appearance
  - Collection of vital signs, including body temperature, blood pressure, heart rate and respiratory rate
  - Examination of head, ears, eyes, nose and throat (HEENT)
  - Examination of skin
  - Auscultation of heart and lungs
- Collection and review of prior and concomitant medications or vaccinations taken prior to start of study (refer to section 6.5 for further details).
- Collection of any unsolicited AEs occurring prior to administration of the study vaccine.

- Blood draw (approximately 10 ml) for Safety Laboratory assessments, measurement of Hepatitis B surface antigen, anti-Hepatitis C virus antibodies, anti-HIV 1 and 2 antibodies and serum pregnancy test (all women).
- Urine sample for Safety Laboratory assessments and drugs-of-abuse testing.

NOTE: A general physical examination is to be performed by a qualified health care practitioner. "Qualified health care practitioner" refers to any licensed health care professional who is permitted by institutional policy to perform physical examinations and who is identified within the Study Staff Signature Log.

Data collected during the Pre-vaccination Screening Clinic Visit must be written in the source document (see section 9.1) and will be captured in the screening CRF Forms. In the event that the individual is determined ineligible for study participation, he/she is considered a screen failure. The reason for screen failure must be documented in the Screening and Enrolment log.

5.2 Vaccination Clinic Visit(s)

This section describes the procedures to be performed at the Vaccination Clinic Visit (Visit 1, Day 1), including: pre-vaccination procedures, enrolment, randomization, prevaccination blood draw, vaccination and post-vaccination procedures.

5.2.1 Pre-vaccination Procedures

During pre-vaccination procedures at Visit 1 (Day 1), the eligibility of the subject will be confirmed based on the inclusion and exclusion criteria listed in section 4.0.

Pre-vaccination procedures at Visit 1 (Day 1) will include the following:

- Review of systems by means of a structured interview that queries the subject as to any complaints the subject has experienced across each organ system.
- Perform physical examination, including but not limited to:
  - Assessment of general appearance
  - Assessment of body weight and collection of vital signs, including body temperature, blood pressure, heart rate, and respiratory rate
  - Examination of head, ears, eyes, nose and throat (HEENT)
  - Examination of skin
  - Auscultation of heart and lungs

- Collection and review of prior and concomitant medications or vaccinations taken, or recalled, since the last visit (refer to section 6.5 for further details).
- Collection of any unsolicited AEs occurring prior to administration of the study vaccine.
- One blood sample (approximately 10 ml) will be drawn from all subjects for serology testing.
- One blood sample (approximately 10 ml) will be drawn from all subjects for baseline Safety Laboratory assessments.
- One urine sample for baseline Safety Laboratory assessments, pregnancy testing (all women) and drugs-of-abuse testing.
- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and volume of blood draws are provided in section 3.5.

NOTE: A general physical examination is to be performed by a qualified health care practitioner. "Qualified health care practitioner" refers to any licensed health care professional who is permitted by institutional policy to perform physical examinations and who is identified within the Study Staff Signature Log.

Data collected during pre-vaccination procedures at Visit 1 must be written in the source document (see section 9.1). In the event that the individual is determined ineligible for study participation, he/she is considered a screen failure. The reason for screen failure must be documented in the Screening and Enrolment log. If the individual is determined to be eligible for the study, he/she can be enrolled into the study.

5.2.2 Enrolment

After an individual is determined to be eligible for study participation, the investigator will enroll the subject into an Electronic Data Capture (EDC) system where the randomization to the treatment group will occur. The Screening Number ceases to be used and remains in the Screening and Enrolment Log only.

If for any reason, after signing the informed consent form (ICF), the subject who is eligible and enrolled fails to be randomized, this is called a randomization failure. In this case the early termination study procedures must be applied. The reason for all randomization failures should be recorded in the Screening and Enrolment Log and in the source document as specified in the Source Data Agreement. The information on subjects

who are randomization failures should be kept distinct from subjects who are screen failures, as described in section 5.1.2 and section 5.2.1.

5.2.3 Randomization

Enrolled subjects will be randomized and automatically assigned a unique Subject ID. The Subject ID will be the subject's unique identification number for all CRFs and associated study documentation that will be used for the duration of the study.

If for any reason, after signing the informed consent form (ICF), the eligible subject is enrolled and randomized but fails to undergo treatment, this is an Early Termination and the reason should be recorded in source document as specified in the Source Data Agreement/Source Data Verification Form. The information on these Early Termination subjects should be kept distinct in the source documentation from randomization failures, which are described in section 5.2.2.

5.2.4 Vaccination

After completing the pre-vaccination procedures at Visit 1 (Day 1), administer the vaccine to the subject according to the procedures described in section 6.3. Observe the blinding procedures described in section 3.3.

5.2.5 Post-vaccination Procedures

The following post-vaccination procedures will be performed at Visit 1 (Day 1):

- After vaccination, the subject will be observed for at least 30 minutes for any immediate solicited and unsolicited AEs and a body temperature measurement at 30 min after vaccination. All safety and body temperature data collected during this time are to be recorded in the subject's source document.
- After vaccination, the subject will be observed for at least 24 hours at the clinic including observation for solicited and unsolicited AEs and body temperature measurements. Body temperature measurements must be performed at 2, 4, 6, 8, 10, 12, 18 and 24 hours after vaccination. All safety and body temperature data collected during this time are to be recorded in the subject's source.
- One blood sample (approximately 10 ml) will be drawn from all subjects at 24 hours after vaccination for Safety Laboratory assessments.
- One urine sample will be collected from all subjects at 24 hours after vaccination for Safety Laboratory assessments.

- From those subjects that signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn in the first 24 hours after vaccination. Details regarding the number and volume of post-vaccination blood draws are provided in section 3.5.

After the initial 24 hours inpatient observation period, a Subject Diary will be used in this study to document solicited and unsolicited AEs until Day 14. The Subject Diary is the only source for collection of solicited AEs after the initial 24 hours inpatient observation period. Therefore, it is critical that the subject completes the Subject Diary correctly.

The following training regarding completion of the Subject Diary must be provided:

- The subject should be trained on how and when to complete each field of the Subject Diary.
- The subject should be trained on how to self-measure local solicited adverse events and body temperature. The measurement of solicited local adverse events is to be performed using the ruler provided by the site.
- The subject should be instructed how to perform body temperature measurement using the thermometer provided by the site. If the subject feels unusually hot or cold during the day, the subject should check their body temperature. If the subject has fever, the highest body temperature observed that day should be recorded in the Subject Diary.

Subject Diary training should be directed at the individual(s) who will perform the measurements of adverse events and who will enter the information into the Subject Diary. This individual may not be the subject, but if a person other than the subject enters information into the Subject Diary, this person's identity must be documented in the Subject Diary. Any individual that writes in the Subject Diary must receive training on completion of the Diary Card at the time of the visit. This training must be documented in the subject's source record.

The site should schedule the next study activity (clinic visit) with the subject.

The subject will receive a written reminder of the next planned study activity. The subject will be reminded to complete the Subject Diary and to contact the site if there are any questions, and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

5.3 Post-vaccination Visit(s)

5.3.1 Subject Diary Reminder, Safety Follow-up and/or Post-vaccination Blood Draw Clinic Visits

Subject Diary reminder, Safety follow-up and/or post-vaccination blood draw clinic visits will be performed on Day 4 (Visit 2), Day 8 (Visit 3), Day 15 (Visit 4), Day 29 (Visit 6), Day 85 (Visit 7), Day 113 (Visit 8) and Day 181 (Visit 9)

At Day 4 (Visit 2) the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. All unsolicited AEs, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. Any concomitant medications or vaccinations associated with those events must also be recorded on the source documents.
- All subjects will be reminded to complete the Subject Diary and to contact the site if there are any questions, and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit. No changes to the Subject Diary should be done at the clinic visit.
- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and volume of blood draws are provided in section 3.5.
- The site should schedule the next study activity (clinic visit) with the subject and the subject will receive a written reminder of the next planned study activity.

At Day 8 (Visit 3) the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. All unsolicited AEs, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. Any concomitant medications or vaccinations associated with those events must also be recorded on the source documents.

- The subject will be reminded to complete the Subject Diary and to contact the site if there are any questions, and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to hospitalization or an emergency room visit. No changes to the Subject Diary should be done at the clinic visit.
- Blood draw (approximately 10 ml) from all subjects for Safety Laboratory assessments.
- Urine sample from all subjects for Safety Laboratory assessments.
- Blood draw (approximately 10 ml) from all subjects for serology testing.

- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and
- volume of blood draws are provided in section 3.5.

  The site should schedule the next study activity (clinic visit) with the subject and the subject will receive a written reminder of the next planned study activity.

At Day 15 (Visit 4) the following procedures will be performed:

- The Subject Diary will be collected and reviewed. No changes to the Subject Diary should be done at the clinic visit. For details on the Subject Diary see sections 3.4.2, and 5.2.5. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. All unsolicited AEs until Day 14, solicited local and systemic AEs persisting at Day 14, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. All concomitant medications or vaccinations associated with those events must also be recorded on the source documents.
- The site should schedule the next study activity (safety phone call) with the subject.
- The subject will receive a written reminder of the next planned study activity. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

At Day 29 (Visit 6) the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. Any solicited local and systemic AEs continuing beyond Day 14, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. All concomitant medications or vaccinations associated with those events must also be recorded on the source documents.

- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and

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- Blood draw (approximately 10 ml) from all subjects for Safety Laboratory assessments.
- Urine sample from all subjects for Safety Laboratory assessments.
- Blood draw (approximately 10 ml) from all subjects for serology testing.

volume of post-vaccination blood draws are provided in section 3.5.

The site should schedule the next study activity (clinic visit) with the subject.

- The subject will receive a written reminder of the next planned study activity. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

At Day 85 and Day 113 (Visit 7 and Visit 8), the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. Any solicited local and systemic AEs continuing beyond Day 14, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. All concomitant medications or vaccinations associated with those events must also be recorded on the source documents.
- The site should schedule the next study activity (clinic visit) with the subject.
- The subject will receive a written reminder of the next planned study activity. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

At Day 181 (Visit 9), the following procedures will be performed:

- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and

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- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. Any solicited local and systemic AEs continuing beyond Day 14, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. All concomitant medications or vaccinations associated with those events must also be recorded on the source documents.
- Blood draw (approximately 10 ml) from all subjects for serology testing.

  volume of post-vaccination blood draws are provided in section 3.5.

  The site should schedule the next study activity (safety phone call) with the subject.
- The subject will receive a written reminder of the next planned study activity. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

5.3.2 Safety Follow-up Calls

Safety follow-up calls will be performed on Day 22 (Visit 5), Day 209 (Visit 10) and Day 271 (Visit 11) and include the following procedures:

- Safety follow-up calls are calls made to the subject by a healthcare professional designated on the site log. These calls will follow a script which will facilitate the collection of relevant safety information. The subject will be interviewed according to the script, and information relating to solicited local and systemic AEs persisting beyond Day 14 and unsolicited adverse events including SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal, and/or NOCD and concomitant medications or vaccinations associated with those events. All safety information described by the subject must be written down in a designated location within the source document and not written on the script used for the telephone call.

- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and

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- The site should schedule the next study activity (clinic visit or study termination visit) with the subject.
- The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

5.4 Unscheduled Visits

An unscheduled visit describes a non-routine study visit triggered by a specific event. These could include anticipated or unanticipated adverse events or interventions.

The following procedures should be carried out for all unscheduled visits:

1. Evaluate the subject's vital signs body temperature, heart rate, and blood pressure and perform a symptom-directed physical examination.
2. Record any observed AEs in the source documents.

3. Record any concomitant medications or vaccinations associated with AEs in the source documents.

5.5 Study Termination Visit

The study termination visit is scheduled on Day 366 (Visit 12). The termination visit is a clinic visit. For visit procedures to be performed for a subject whose planned study participation ends prematurely, please see section 5.5.1.

At the Study Termination clinic visit the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit.
- The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present.
- Medically attended AEs, SAEs, NOCDs, or AESIs will be recorded on source documents.
- All medications taken or vaccines received will also be recorded on the source documents.
- The site will review with the subject the plan of when information relating to the subject's participation in the study may be available (e.g., study results, treatment assignments). It will also be discussed how information relating to the subject's participation in the study will be shared with the subject's healthcare provider, if the subject chooses to share this information.
- The site will complete the termination CRF page and this will mark the completion of the subject's participation in the study.

5.5.1 Early Termination Visit

The date of termination is the date of the last contact in which the subject's health status was assessed or, in cases where the subject does not agree to any further safety follow-up, it is the date consent is withdrawn. This date should be recorded on the appropriate CRF page.

When a subject is withdrawn from treatment or withdraws from the study, the investigator will notify the Sponsor and, when possible, will perform the procedures listed below.

The reason(s) for the early termination must be included in the subject's source documentation. If the Early Termination Visit is a telephone call, collect as much information as possible. Early Termination Visits include subjects who were randomized but not treated.

At the clinic visit or during the telephone call, the following procedures should be performed, when possible:

- Collection and review of Subject Diary (if not already collected).
- Interview of subject to collect unsolicited adverse events, medically attended AEs, AEs leading to withdrawal, SAEs, AESIs, and NOCD.
- Interview of subject to collect concomitant medications and/or vaccinations.
- Symptom-directed physical assessment, at least including measurement of vital signs (body temperature, respiratory rate, blood pressure, heart rate) and a check of general appearance (in case of clinic early termination visit).
- Draw a blood sample (approximately 10 ml) and a urine sample for Safety Laboratory assessment (in case of clinic early termination visit).
- The site will review with the subject the plan of when information relating to the subject's participation in the study may be available (e.g., study results, treatment assignments). It will also be discussed how information relating to the subject's participation in the study will be shared with the subject's healthcare provider, if the subject chooses to share this information.
- The site will complete the appropriate CRF page and this will mark the completion of the subject's participation in the study.

6.0 TREATMENT OF SUBJECTS

All vaccines associated with this study are to be stored separately from other vaccines and medications in a secure location under appropriate storage conditions with temperature monitoring. **All vaccines associated with this study must be checked for expiration date prior to use. Expired vaccines must not be administered to subjects.**

6.1 Study Vaccine(s)

The term 'study vaccine' refers to those vaccines provided by the Sponsor, which will be evaluated as part of the study objectives. The study vaccines specific to this study are described in Table 6.1-1.

Table 6.1-1: Study Vaccine Composition

Group A (Control) Meningococcal C-CRM$_{197}$ Conjugate Vaccine	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM$_{197}$ protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
Sodium Chloride	3.5 mg
Sterile water for injection, up to	0.5 ml

Group B (12.5µg LHD153R) - MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM$_{197}$ protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide/LHD153R Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
LHD153R	12.5 µg
Sodium Chloride	3.4 mg

Histidine	0.1 mg
Tris	30 µg
Sterile water for injection, up to	0.5 ml
Group C (25 µg LHD153R) - MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM$_{197}$ protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide/LHD153R Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
LHD153R	25 µg
Sodium Chloride	3.4 mg
Histidine	0.2 mg
Tris	61 µg
Sterile water for injection, up to	0.5 ml

Group D (50µg LHD153R) - MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM$_{197}$ protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg

Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide/LHD153R Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
LHD153R	50 µg
Sodium Chloride	3.2 mg
Histidine	0.4 mg
Tris	121 µg
Sterile water for injection, up to	0.5 ml
Group E (100µg LHD153R) - MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM$_{197}$ protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide/LHD153R Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
LHD153R	100 µg
Sodium Chloride	2.9 mg
Histidine	0.8 mg
Tris	243 µg
Sterile water for injection, up to	0.5 ml

6.2 Non-Study Vaccines

The term 'non-study vaccine' refers to those vaccines which will be intentionally given to study subjects but not formally included in the analysis of study objectives.

No non-study vaccines are planned for this study. Any non-study vaccines administered during the study conduct will be captured in the CRF as concomitant medications and/or vaccinations.

6.3 Vaccine Preparation and Administration

The investigator or designee will be responsible for oversight of the administration of vaccine to subjects enrolled in the study according to the procedures stipulated in this study protocol. All vaccines will be administered only by unblinded personnel who are qualified to perform that function under applicable local laws and regulations for the specific study site.

The vaccine components will be provided in 5 separate kits (i.e. one for the control and one for each of the 4 dosage groups). The vaccine components must be mixed prior to vaccination taking into account the appropriate aseptic procedures. Detailed vaccine preparation and administration instructions, including the maximal administration period, will be provided to investigators prior to study start and must be filed in the Investigator Site File.

PRECAUTIONS TO BE OBSERVED IN ADMINISTERING STUDY VACCINE:

- Prior to vaccination, subjects must be determined to be eligible for study vaccination and it must be clinically appropriate in the judgment of the investigator to vaccinate. Eligibility for vaccination prior to first study vaccine administration is determined by evaluating the entry criteria outlined in protocol sections 4.0.

- Study vaccines must not be administered to individuals with known hypersensitivity to any component of the vaccines.

- Standard immunization practices are to be observed and care should be taken to administer the injection intramuscularly. Before administering vaccine, the vaccination site is to be disinfected with a skin disinfectant (e.g., 70% alcohol). Allow the skin to dry. **DO NOT inject intravascularly**.

- As with all injectable vaccines, trained medical personnel and appropriate medical treatment must be readily available in case of anaphylactic reactions following vaccine administration. For example, epinephrine 1:1000, diphenhydramine, and/or other medications for treating anaphylaxis should be available.

6.4 Vaccine Administration Error or Overdose of Vaccine

Vaccine administration error is defined as receiving a dose of study vaccine that was not reconstituted as instructed or administered by a different route from the intended route of administration. An overdose of study vaccine (whether accidental or intentional) is defined when a dosage higher than the recommended dosage is administered in one dose of study vaccine.

Any vaccine administration error or overdose of study vaccine detailed in this protocol must be reported as an adverse event, and if the vaccine administration error or overdose is associated with a serious adverse event, it must be reported as such within 24 hours to the Sponsor.

6.5 Prior and Concomitant Medications and Vaccines

All medications, vaccines and blood products taken or received by the subject within 180 days prior to the start of the study are to be recorded in the appropriate CRF.

Medications taken for prophylaxis are those intended to prevent the onset of symptoms. Medications taken for treatment are intended to reduce or eliminate the presence of symptoms that are present.

NOTE: Use of antipyretics/analgesics within 24 hours prior to vaccine administration is a reason to delay study vaccination (see section 4.3).

Concomitant medications include all medications (including vaccines) taken by/administered to the subject at and after enrolment and must be documented in the appropriate CRF.

When recording concomitant medications/vaccines, they should be checked against the study entry criteria in section 4.0, to ensure that the subject should be enrolled in the study.

6.6 Vaccine Supply, Labeling, Storage and Tracking

The Sponsor will ensure the following:

- Supply the study vaccines.
- Appropriate labeling of all study vaccines provided that complies with the legal requirements of each country where the study is to be performed.

The investigator must ensure the following:

- Acknowledge receipt of the study vaccines by a designated staff member at the site, including:
  - Confirmation that the vaccines were received in good condition
  - Confirmation to the Sponsor of the temperature range during shipment from the Sponsor to the investigator's designated storage location
  - Confirmation by the Sponsor that the vaccines are authorized for use.
- Proper storage of the study vaccines, including:
  - Storage in a secure, locked, temperature-controlled location.
  - Proper storage according to the instructions specified on the labels.
  - Appropriate record keeping and inventory of the study vaccines, including regular documentation of adequate storage temperature.
- Appropriate use of the study vaccines, including:
  - No use of vaccines prior to receipt of authorization for use from the Sponsor.
  - Use only in accordance with the approved protocol.
  - Proper handling, including confirmation that the vaccine has not expired prior to administration.
  - Appropriate documentation of administration of vaccines to study subjects including:
    - Date, dosage, batch/lot numbers, expiration dates, unique identifying numbers assigned to subjects and study vaccines, and time of vaccine administration. This information will be maintained in an accountability log that will be reviewed by the site monitor.
    - Reconciliation of all vaccines received from the Sponsor. Reconciliation is defined as maintaining records of which and how many vaccines were received, which vaccines were administered to subjects, which vaccines were destroyed at the site, and which vaccines were returned to the Sponsor, as applicable.
- Proper adherence to the local institutional policy with respect to destruction of study vaccines.

- Complete record keeping of vaccine use, wastage, return or destruction, including documentation of:
  - Copy of the site's procedure for destruction of hazardous material.
  - Number of doses destroyed, date of destruction, destruction code (if available), method of destruction, and name of individual performing destruction.

Vaccines that have been stored differently from the manufacturer's indications **must not** be used unless the Sponsor provides written authorization for use. In the event that the use cannot be authorized, the Sponsor will make every effort to replace the vaccine supply. All vaccines used in conjunction with this protocol must be stored separately from normal hospital/practice stocks to prevent unintentional use of study vaccines outside of the clinical study setting.

Monitoring of vaccine accountability will be performed by the study monitor during site visits and at the completion of the study.

At the conclusion of the study, and as appropriate during the course of the study, the investigator must ensure that all unused study vaccines, packaging and supplementary labels are destroyed locally (upon approval from Sponsor) or returned to the Sponsor.

7.0 ASSESSMENTS

7.1 Safety Assessment

The measures of safety used in this study are based on previous study data and based on comparable routine clinical/laboratory procedures. They include a close vigilance for, and stringent reporting of selected local and systemic adverse events routinely monitored in vaccine studies as indicators of reactogenicity.

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

The period of observation for AEs extends from the time the subject signs informed consent until he or she completes the specified safety follow-up period (Day 366) or terminates the study early (whichever comes first). AEs occurring after the informed consent form is signed but prior to receiving study vaccine/product will be documented as an adverse event and recorded within the source documents. However, any AEs occurring prior to receipt of any study vaccine will be analyzed separately from “treatment emergent” AEs (AEs occurring after administration of the first study vaccine).

Adverse events are collected as either solicited or unsolicited adverse events. Solicited events are derived from organized data collection systems, such as Subject Diaries or interview.

7.1.1 Solicited Adverse Events

The term “reactogenicity” refers to solicited signs and symptoms (“solicited adverse events”) occurring in the hours and days following a vaccination, to be collected by the subject after the first 24 hours inpatient observation period at Day 1until Day 14, using a pre-defined Subject Diary.

The following solicited adverse events are included in the Subject Diary. Each adverse event is to be assessed using the scoring system shown in Appendix A (Solicited Local AEs) and Appendix B (Solicited Systemic AE):

Solicited Local Adverse Events

Solicited local AEs include:

- injection site erythema
- injection site induration
- injection site pain
- injection site swelling **Solicited Systemic Adverse Events**

Solicited systemic AEs include:

- body temperature ≥38.0°C (as measured orally)
- loss of appetite
- nausea
- fatigue
- generalized myalgia
- generalized arthralgia
- headache
- chills
- vomiting
- diarrhea
- generalized rash
- urticaria

Other Solicited Data

Other solicited data collected per Subject Diary include:

- Use of analgesics/antipyretics recorded as “absent” or “present” and summarized by “for treatment” or “for prophylaxis”
- Body temperature as recorded daily, ideally at same time, by the oral route

The study staff must review the data entered into the Subject Diary as described in sections 3.4.2 and 5.3.1.

NOTE: Any solicited adverse event that meets any of the following criteria must be entered into the subjects' source documents (see section 9.1) and also as an adverse event in the appropriate CRF:

- Solicited local or systemic adverse event that continues beyond Day 14 after vaccination.
- Solicited local or systemic adverse event that leads to a visit to a healthcare provider (medically attended adverse event, see section 7.1.3).
- Solicited local or systemic adverse event leading to the subject withdrawing from the study or the subject being withdrawn from the study by the investigator (adverse event leading to withdrawal, see section 7.1.3).
- Solicited local or systemic adverse event that otherwise meets the definition of a serious adverse event (see section 7.1.4).

7.1.2 Unsolicited Adverse Events

An unsolicited adverse event is an adverse event that was not solicited using a Subject Diary and that was spontaneously communicated by a subject who has signed the informed consent.

7.1.3 Evaluation of Adverse Events

Every effort should be made by the investigator to evaluate safety information reported by a subject for an underlying diagnosis and to capture this diagnosis as the event in the AE page. In other words, the practice of reporting only symptoms (e.g., "cough" or "ear pain") are better reported according to the underlying cause (e.g., "asthma exacerbation" or "otitis media").

The severity of events reported on the appropriate CRF page will be determined by the investigator as:

Mild: transient with no limitation in normal daily activity.
Moderate: some limitation in normal daily activity.
Severe: unable to perform normal daily activity.

The relationship of the study treatment to an AE will be determined by the investigator based on the following definitions:

1. Not Related

The AE is not related to an investigational vaccine if there is evidence that clearly indicates an alternative explanation. If the subject has not received the vaccine, the timing of the exposure to the vaccine and the onset of the AE are not reasonably related in time, or other facts, evidence or arguments exist that reasonably suggest an alternative explanation, then the AE is not related.

2. Possibly Related

The administration of the investigational vaccine and AE are considered reasonably related in time and the AE could be explained by exposure to the investigational vaccine or by other causes.

3. Probably Related

Exposure to the investigational vaccine and AE are reasonably related in time and no alternative explanation has been identified.

The relationship of the study treatment to an unsolicited AE will be determined by the investigator.

Note: solicited AEs will not be evaluated for relationship to study treatment. Grading for severity of solicited local and systemic AEs is described in Appendix A and Appendix B.

Adverse events will also be evaluated by the investigator for the co-existence of any of the other following conditions:

- "Medically attended adverse event": an adverse event that leads to a visit to a healthcare provider.
- "New onset of chronic disease" (NOCD): an adverse event that represents a new diagnosis of a chronic medical condition that was not present or suspected in a subject prior to study enrolment.
- AEs leading to withdrawal: adverse events leading to study or vaccine withdrawal.

All AEs, regardless of severity, will be monitored until resolution or until the investigator assesses them as chronic or stable. All subjects experiencing AEs - whether considered associated with the use of the study vaccine or not - must be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible.

7.1.4 Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose results in one or more of the following:

- Death.
- Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe.
- Required or prolonged hospitalization.
- Persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions).
- Congenital anomaly/or birth defect.
- An important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

Adverse events which do not fall into these categories are defined as non-serious.

It should be noted that a severe adverse event need not be serious in nature and that a serious adverse event need not, by definition, be severe.

Serious adverse events will be captured both on the Vaccines Serious Adverse Event (VSAE) form as well as on the appropriate CRF page. All SAEs will be evaluated by the investigator for relationship of the event to study vaccine. SAEs that are judged to be possibly or probably related to the study vaccine should be reported to the Sponsor as related/suspected events.

The relationship of the study treatment to an SAE will be determined by the investigator based on the following definitions:

1. Related/suspected

The SAE is judged by the investigator to be possibly or probably related to the study vaccine on the appropriate CRF page (see section 7.1.3).

2. Not Related

The SAE is not related if exposure to the study vaccine has not occurred, **or** the occurrence of the SAE is not reasonably related in time, **or** the SAE is considered unlikely to be related to use of the study vaccine, i.e., there are no facts (evidence) or arguments to suggest a causal relationship.

The relationship of the study vaccine to an SAE will be determined by the investigator.

In addition, SAEs will be evaluated by the Sponsor or designee for "expectedness." An unexpected AE is one that is not listed in the current Summary of Product Characteristics or the Investigator's Brochure or an event that is by nature more specific or more severe than a listed event.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the appropriate CRF. If the onset of an event occurred before the subject entered the study (e.g., any pre-planned hospitalization for conditions like cosmetic treatments or for non-emergency routine visits for a pre-existing condition), the hospitalization would not lead to an AE being classified as serious unless, in the view of the investigator, hospitalization was prolonged as a result of participation in the clinical study or was necessary due to a worsening of the pre-existing condition.

7.1.4.1 Adverse Events of Special Interest

Certain adverse events of special interest (AESIs) are monitored after the administration of immunostimulatory agents. All subjects enrolled in this study will be monitored for AESIs for the entire follow-up period. The AESIs will be defined according to MedDRA preferred terms. The investigator will be provided with a list of AESIs prior to study start. Receipt of this list will be notified and stored, along with the list of AESIs, in the Investigator Site File. During the course of the trial the list of AESIs may change. If this occurs, the investigators will be advised of the change and confirmation of receipt will be documented. The updated list of AESIs and documentation of receipt are also stored in the Investigator Site File. The occurrence of any of these adverse events will be treated as a serious adverse event (SAE), meeting the criterion of a "medically important event."

Subjects will be assessed for diagnosis of an AESI at the following visits:

- Pre-vaccination clinic visit (Day -28 to Day -3)
- Visit 1 (Day 1, pre-vaccination)
- Visit 2 (Day 4)

- Visit 3 (Day 8)
- Visit 4 (Day 15)
- Visit 5 (Day 22; Safety Follow-Up Call)
- Visit 6 (Day 29)
- Visit 7 (Day 85)
- Visit 8 (Day 113)
- Visit 9 (Day 181)
- Visit 10 (Day 209; Safety Follow-Up Call)
- Visit 11 (Day 271; Safety Follow-Up Call)
- Visit 12 (Day 366; Study Termination Visit)

At these visits a qualified health care practitioner listed on the site's responsibilities and delegation logs will conduct a review of organ systems and a targeted physical exam and will evaluate subjects for any new signs or symptoms that could indicate one of the AESIs as specified in the list of AESIs stored in the Investigator Site File. They will also interview the subject about recent medical history and any new diagnosis that could indicate an AESI. Medical records related to any new medical event or diagnosis will be requested, reviewed by the site staff, and recorded in the subject's source documents.

A diagnosis of an AESI will be reported in the same manner and time frame as an SAE using the VSAE form. The investigator must notify GSK within 24 hours. The AESI diagnosis, as well as any medications taken to treat the condition, will be recorded in the subject's source documents and on the appropriate CRF.

7.1.5 Methods for Recording Adverse Events and Serious Adverse Events

All findings regarding Adverse Events must be reported on the appropriate CRF page and on the VSAE form, if applicable, which is part of the Investigator Site File. All findings in subjects experiencing AEs must be reported also in the subject's source document.

All SAEs which occur during the course of the study, whether considered to be associated with the study vaccination or not, must be reported **within 24 hours of the site becoming aware of the event** to GSK or its designee. Specific instructions and contact details for collecting and reporting SAEs to GSK will be provided to the investigator.

All SAEs are also to be documented on the appropriate CRF page. Any medication or other therapeutic measures used to treat the AE will be recorded on the appropriate CRF(s) in addition to the outcome of the AE.

After receipt of the initial report, representatives of GSK or its designee will contact the investigator if it is necessary to obtain further information for assessment of the event.

All SAEs must be reported by the investigator to his/her corresponding EC and applicable regulatory authorities in accordance with institutional policy/regulatory requirements and adequate documentation of this notification must be provided to the Sponsor.

GSK or its designee must also comply with the applicable regulatory requirement(s) related to the reporting of suspected unexpected serious adverse vaccine reactions (also known as SUSARs) to the regulatory authority(ies) and the IRB/EC. If a SUSAR or other safety signal relating to use of one of the study vaccines is reported to GSK or its designee, the Sponsor will communicate the information to the investigator and the investigator will be responsible for submitting this information to the EC and other relevant authorities.

7.1.5.1 Post-Study Events

Any suspected SAE that occurs outside of the protocol-specified follow-up period or after the end of the study but considered to be caused by the study vaccine must be reported to GSK or its designee. These SAEs will be processed by GSK or its designee as during the course of the study, until 3 months after the last scheduled study visit. Instructions and contact details for collecting and reporting these suspected SAEs will be provided to the investigator.

7.1.6 Pregnancies

To ensure subjects' safety, each pregnancy in a subject after study vaccination must be reported to GSK within 72 hours of the site learning of its occurrence. If the subject agrees to submit this information, the pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if intended duration of safety follow-up for the study has ended.

Pregnancy data must be recorded on a Pregnancy Report CRF (initial report) and Pregnancy Follow-Up CRF (outcome report).

Any pregnancy outcome meeting the definition of a SAE (see section 7.1.4) must also be reported on the VSAE Report Form.

7.1.7 Safety Laboratory Measurements

Blood and urine samples will be collected from all subjects at the Pre-vaccination Screening, at Visit 1 (pre-vaccination and 24 hours after vaccination), at Visit 3 and at Visit 6 as outlined in Time and Events Table 3. The blood safety laboratory assessments will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, liver function tests (ALT, AST), a complete blood count and C-reactive protein. The urine safety laboratory assessments will include protein, glucose and red blood cells. An additional blood and urine sample will be collected in case of a clinic Early Termination Visit as outlined in section 5.5.1.

All testing will be conducted by qualified and certified laboratories. The Investigator **must** assess all safety laboratory results. Abnormal laboratory values must be classified by the Investigator as clinically significant or not. Abnormal laboratory values that are considered clinical significant will be defined following the FDA CBER Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" dated September 2007, or the institution's normal ranges if they differ from CBER guidance. Please see Appendix C, D and E for further details on the Toxicity Grading Scales according to CBER.

Retesting may be performed in case of abnormal values per guidance of the investigator.

7.2 Efficacy Assessment

Efficacy measurement will not be performed as part of this study.

7.3 Immunogenicity Assessment

The measures to assess the primary and secondary immunogenicity endpoints for this study are standard, i.e., widely used and generally recognized as reliable, accurate, and relevant (able to describe the quality and extent of the immune response).

The assay's used in this study to assess the primary and immunogenicity endpoints are human serum bactericidal assay (hSBA) and ELISA specific for MenC

The hSBA is a functional measure of the ability of specific antibodies, in conjunction with human complement, to kill MenC indicator strains, and is widely used and generally recognized as the serological correlate of protection. The specific ELISA will be used to

measure the induction of antibodies directed against MenC following vaccination with the study vaccines.

Blood samples (approximately 10 ml) to obtain serum for hSBA and ELISA assays will be collected at Day 1, Day 8, Day 29 and Day 181 (refer to section 3.5 for detailed specimen collection procedures).

Testing will be conducted by a GSK or designated laboratory in a blinded manner towards the treatment group. Laboratory contact details are listed in the Protocol Ancillary Document.

All data will be captured at the laboratory and transferred via Electronic Data Transfer (EDT)

Details on all blood sample handling steps are described in the Clinical Specimen Lab Manual provided to the study site.

7.4 Exploratory Measurements

In those subjects who agree to a separate Informed Consent, additional blood samples will be collected at Day 1, Day 4, Day 8, Day 29 and Day 181 for exploratory measurements. The purpose of these exploratory measurements is to assess the systemic exposure of LHD153, to further delineate vaccine induced antigen specific immune responses and to evaluate biomarkers that may be predictive for safety and/or innate immune activation.

All exploratory measurements will be conducted by a GSK or a designated laboratory. Laboratory contact details are listed in the Protocol Ancillary Document.

Exploratory measurements may be performed after the Clinical Study Report (CSR) has been completed, in which case these data will be submitted as an addendum to the CSR.

Systemic exposure of LHD153

Systemic exposure of LHD153 will be assessed by analyzing LHD153 blood plasma levels at Day 1 (baseline, 1, 2, 4, 8 and 24h after vaccination) and Day 4 using LC/MS/MS. Time-points for assessment of clinical exposure of LHD153 have been selected based on non-clinical data in dogs and rats.

Vaccine-induced antigen-specific immune responses

The frequency of B cells specific for MenC polysaccharide and CRM_{197} will be determined by enzyme-linked immunosorbent spot (ELISPOT) at Day 1, Day 8, Day 29 and Day 181 in order to evaluate the baseline specific B-cell frequency (Day 1), the peak

of plasmablast responses (Day 8), the peak of B cell memory responses (Day 29), and the persistence of memory B cell responses (Day 181).

Subsequently, the diversity of the antigen specific B-cell repertoire will be analyzed in a selected subset of subjects. The selection of the subset will be based on the most pronounced response to the study vaccines when compared to baseline as determined by the primary and secondary immunogenicity assessment.

The diversity of the elicited B-cell receptors will be assessed through sequence analysis of complementary DNA (cDNA) generated from immunoglobulin (Ig) messenger RNA (mRNA). The Ig cDNAs will be analyzed from antigen-specific B cells obtained at Day 1, Day 29 and/or Day 181 and plasmablasts isolated at Day 8. The analysis of the B-cell receptor diversity does not have the intent nor the capability to identify or rule out any genetic modifications in the RNA or DNA that are presumably linked to disease or predisposition to disease.

The frequency of T cells specific for the CRM_{197} protein at baseline (Day 1), at Day 8 and at Day 29 after vaccination with the study vaccines will be determined by FACS analysis using intracellular staining with a panel of cytokines and surface markers to identify cell populations.

Early Markers for Safety and Innate immune activation

The evaluation of potential biomarkers of safety and innate immune activation will be performed on blood specimens collected at Day 1 (baseline, 6h and 24h after vaccination) and Day 4.

The vaccine-induced production of inflammatory cytokines and chemokines will be monitored on serum samples using a commercially available electrochemoluminescence assay for a panel of pro-inflammatory cytokines and chemokines, including Eotaxin, Eotaxin-3, GM-CSF, IFN-g, IL-1a, IL-1b, IL-10, IL-12 p70, IL-12/IL-23p40, IL-13, IL15, IL-16, IL-17A, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-8 (HA), IP-10, MCP-1, MCP-4, MDC, MIP-1a, MIP-1b, TARC, TNF-a, TNF-b, VEGF.

The vaccine-induced expression of genes and gene families will be monitored on whole blood samples using of RNA microarrays by existing technologies. The RNA micro array analysis does not have the intent nor the capability to identify or rule out any genetic modifications in the RNA or DNA that are presumably linked to disease or predisposition to disease.

The vaccine-induced changes in myeloid (e.g. monocytes and dendritic cells) and lymphoid (e.g. NK cells, NKT cells) cell numbers and their activation status will be assessed using flow cytometry.

8.0 STATISTICAL CONSIDERATIONS

8.1 Endpoints

8.1.1 Primary Endpoint(s)

8.1.1.1 Primary Safety Endpoint(s)

The measures for assessing safety and tolerability (by vaccine group within each cohort and by LHD153R adjuvant dosage group overall) are as follows:

- The frequency and percentage of subjects with solicited local and systemic AEs through Day 14. Time intervals after vaccination that will be summarized are:30 minutes post-vaccination, Days 1-4 (without 30 minutes), Days 5-8, Days 8-14, Days 1-8 (without 30 minutes) and Days 1-14 (without 30 minutes).
- The frequency and percentage of subjects with any unsolicited AEs from the day of vaccination (Day 1) to Day 14.
- The frequency and percentage of subjects with SAEs, medically attended AEs, AEs leading to study withdrawal, NOCDs, AESIs for the following time periods: day of signed informed consent until study completion (Day 366), day of vaccination (Day 1) to Day 29, and Day 29 to study completion (Day 366).
- The absolute values and changes in hematology, chemistry, and urinalysis parameters (see section 7.1.7).
- The frequency and percentage of subjects with abnormal laboratory parameter values

as classified by investigator normal ranges (low, normal, high) and as classified by CBER toxicity grading scales, when available. **8.1.1.2 Primary Efficacy Endpoint(s)**

Not applicable.

8.1.1.3 Primary Immunogenicity Endpoint(s)

The primary immunogenicity endpoints are the GMTs measured by hSBA directed against MenC from samples collected on Day 1 (baseline, before vaccination) and Day 29 as well as the GMR of the titers (Day 29 / Day 1).

8.1.2 Secondary Endpoint(s) 8.1.2.1

Secondary Safety Endpoint(s)

Not applicable.

8.1.2.2 Secondary Efficacy Endpoint(s)

Not applicable.

8.1.2.3 Secondary Immunogenicity Endpoint(s)

The secondary immunogenicity endpoints are:

- GMTs and corresponding GMRs measured by hSBA directed against MenC for samples collected at Day 8 and Day181.
- Percentage of subjects with hSBA seroresponse at Days 8, 29, and 181. Seroresponse is defined as a post vaccination hSBA ≥8 for subjects with a baseline hSBA <4 or have an increase of at least 4 times the baseline hSBA level for subjects with prevaccination hSBA ≥4.
- Antibody geometric mean concentrations (GMCs) against MenC measured by ELISA for samples collected on Days 1 (baseline, prior to vaccination), 8, 29, and 181.
- The percentage of subjects with at least a 4-fold increase in antibody concentrations to MenC as measured by ELISA on Day 8, 29, and 181 relative to baseline (Day 1).

8.1.3 Exploratory Endpoint(s)

The exploratory endpoints are based on results of testing which may not be performed until after the study report has been finalized and will be further refined prior to testing. They include the following:

- Serum concentration of LHD153 at Day 1 baseline (prior to vaccination), Day 1 (1h , 2h, 4h, 8h, and 24h after vaccination), Day 4 by LC-MS/MS.
- Frequency of MenC polysaccharide-specific and CRM_{197}-specific B cells at Day 1 (baseline), Day 8, Day 29, and Day 181 by ELISPOT.

- Diversity of MenC polysaccharide-specific B-cell repertoire at Day 1 (baseline), Day 8, Day 29, and Day 181 by immunoglobulin cDNA sequencing.
- Frequency and quality of T cells specific for CRM_{197} at Day 1 (baseline), Day 8, and Day 29 by flow cytometry analysis using intracellular staining with a wide panel of cytokines and surface markers to identify cell populations.
- Serum concentrations of a panel of 30 chemokines and cytokines at Day 1 baseline (prior to vaccination), Day 1 (6h and 24h after vaccination), Day 4, and Day 8 by multiplex Electro-chemo-luminescence based assay.
- Gene expression profile in whole blood at Day 1 baseline (prior to vaccination), Day 1 (6h and 24h after vaccination), Day 4, and Day 8 by RNA micro array analysis.
- Number and activation status of myeloid and lymphoid cell populations at Day 1 baseline (prior to vaccination), Day 1 (24h after vaccination), Day 4 and Day 8 by flow cytometry.

8.2 Success Criteria

The study has no formal statistical hypotheses and will not be declared positive or negative according to given rules. The selection of an appropriate LHD153R adjuvant dosage for future studies will be determined by the joint evaluation of the immunogenicity and safety profiles of each dosage group. **8.2.1 Success Criteria for Primary Objective(s)** Not applicable.

8.2.2 Success Criteria for Secondary Objective(s)

Not applicable.

8.3 Analysis Sets

8.3.1 All Enrolled Set

All screened subjects who provide informed consent and provide demographic and/or baseline screening assessments, regardless of the subject's randomization and treatment status in the study and received a Subject ID.

8.3.2 All Exposed Set

All subjects in the enrolled set who receive a study vaccination.

8.3.3 Safety Set

Safety Set (solicited adverse events and other solicited reactions)

All subjects in the Exposed Set who:

- Provide post vaccination reactogenicity data.

Safety Set (unsolicited adverse events)

All subjects in the Exposed Set who:

- Have post-vaccination unsolicited adverse event records.

Safety Set (overall)

All subjects in the Exposed Set who:

- Have either post-vaccination adverse event or reactogenicity records.

Subjects will be analyzed as "treated" (i.e., according to the vaccine a subject received, rather than the vaccine to which the subject may have been randomized).

8.3.4 Full Analysis Set (FAS) Efficacy/Immunogenicity Set

All subjects in the Enrolled Set who:

- Receive a study vaccination AND provide efficacy/immunogenicity data at relevant time points.

FAS sets will be analyzed "as randomized" (i.e., according to the vaccine a subject was designated to receive, which may be different from the vaccine the subject actually received).

8.3.5 Per Protocol (PP) Set Efficacy/Immunogenicity Set

All subjects in the FAS efficacy/immunogenicity set who:

- Are not excluded due to reasons (see section 8.3.8) defined prior to unblinding or analysis.

PPS are subsets of FAS and should always be defined even if the objectives do not require it.

Examples for subjects excluded due to other reasons than protocol deviations are:

- Subjects who withdrew informed consent.
- Premature withdrawal due to an adverse event.

Exclusions need to be considered by objective/time point, i.e., sometimes not all data of a subject but only part of the subject's data will be removed from the PPS analysis.

8.3.6 Other Analysis Sets

All subjects in the Enrolled Set who consent to additional blood draws, receive a study vaccination AND provide exploratory assay data at relevant time points will be included in an exploratory assay subset.

8.3.7 Subgroups

Selected immunogenicity analyses may be provided based on seropositivity status at baseline.

8.3.8 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. A protocol deviation may be a reason to remove data from an analysis set at the time of analysis. Reportable protocol deviations will be defined as exclusionary from the analysis according to protocol objectives and endpoints, which will be specified in the Statistical Analysis Plan. In some cases exclusion of data may be due to a reason other than a protocol deviation, e.g. early termination.

8.4 Statistical Analysis Plan

This section provides a summary of the statistical methodology to be used. A more detailed description of analysis methods will be provided in a separate Statistical Analysis Plan which may also include additional exploratory analyses not explicitly mentioned in the following sections.

8.4.1 Analysis of Demographic and Baseline Characteristics

Descriptive statistics (number of non-missing observations, mean, standard deviation, median, minimum and maximum) for age, height and weight at enrolment will be calculated overall and by vaccine group and LHD153R adjuvant dosage.

Distributions of subjects by sex and ethnic origin will be summarized overall and by vaccine group and LHD153R adjuvant dosage.

8.4.2 Analysis of Primary Objective(s)

8.4.2.1 Analysis of Primary Safety Objective(s)

Safety of the study vaccines will be assessed in all subjects in terms of the frequency and percentage of reported AEs as well as by changes in clinical laboratory values.

8.4.2.1.1 Analysis of Extent of Exposure

The frequency and percentage of subjects with vaccinations will be summarized by vaccine group and LHD153R adjuvant dosage, by cohort and overall, for the Enrolled Set.

8.4.2.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events

All solicited adverse events will be summarized according to defined severity grading scales. Use of medication to prevent/treat fever will be summarized according to frequencies and percentages reporting “Yes” and “No”.

Frequencies and percentages of subjects experiencing each adverse event will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic adverse event overall and at each time point will also be presented.

Post-vaccination solicited adverse events reported from Day 1 to Day 14 will be summarized for the intervals Day 1-4 (without 30 minutes), Day 5-8, Day 1-8 (without 30 minutes), Day 8-14 and Day 1-14 (without 30 minutes) by maximal severity and by vaccine group and LHD153R adjuvant. The severity of solicited local adverse events, including injection-site erythema, swelling and induration will be summarized according to categories based on linear measurement: 25-50 mm, 51-100 mm, > 100 mm.

Injection site pain and systemic reactions (except fever) occurring up to Day 14 will be summarized according to “mild”, “moderate” or “severe”.

Each solicited local and systemic adverse event will also be further summarized as “none” versus “any”.

Implausible measurements (for further definition see Statistical Analysis Plan) will be left out of the analysis.

Use of antipyretics and analgesics will be summarized by frequency by type of use (prophylactic versus treatment) and percentage of subjects reporting use. The influence of

antipyretics and analgesics use on the occurrence of specific adverse events (e.g., fever, pain) will be assessed.

Body temperature will be summarized by 0.5 °C and 1.0 °C increments from 36.0 °C up to ≥40 °C.

8.4.2.1.3 Analysis of Unsolicited Adverse Events

This analysis applies to all adverse events occurring during the study, judged either as probably related, possibly related, or not related to vaccination by the investigator, recorded in the CRF, with a start date on or after the date of first vaccination. AE starting prior to the first vaccination will only be listed. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class.

All reported adverse events, as well as adverse events judged by the investigator as at least possibly related to study vaccine, will be summarized according to system organ class and preferred term within system organ class. These summaries will be presented by vaccination group and LHD153R adjuvant dosage for each cohort and by interval of study observation. When an adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted.

Separate summaries will be produced for the following categories:

- Serious adverse events.
- Adverse events that are possibly or probably related to vaccine.
- Adverse events of special interest.
- New onset of chronic disease.
- Adverse event leading to withdrawal.
- Adverse events leading to a medically attended visit.
- Adverse event by data source.

Data listings of all adverse events will be provided by subject. In addition, adverse events in the categories above will be provided as listed data.

8.4.2.1.4 Analysis of Safety Laboratory Values

The investigator must review all safety laboratory results (see Section 7.1.7). Abnormal laboratory values and clinically significant changes in values from pre-vaccination (Screening Visit) will be assessed, using medical judgment, based on the FDA CBER Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" dated September 2007, or the institution's normal ranges if they differ from CBER guidance. Please see Appendix C, D and E for further details.

The following information will be provided:

- Change in absolute laboratory value from pre-vaccination (Screening Visit) and Day 1 (Visit 1) baseline to Day 1 (24 hours after vaccination), Day 8 (Visit 3) and Day 29 (Visit 6) after vaccination.
- The classification of laboratory values and/or their changes from pre-vaccination according to the CBER toxicity grading scale.
- 3 x 3 shift tables by visit using the categorization of laboratory values according to institutional normal reference ranges (below, within, above).

8.4.2.2 Analysis of Primary Efficacy Objective(s)

Not applicable.

8.4.2.3 Analysis of Primary Immunogenicity Objective(s)

8.4.2.3.1 Statistical Hypotheses

There are no statistical hypotheses associated with the primary immunogenicity objectives. All analyses are descriptive.

8.4.2.3.2 Analysis Sets

The primary immunogenicity analyses will be based on the per-protocol set (PPS) at Day 29. The primary analyses will be repeated using the Full Analysis Set (FAS) as a measure of the sensitivity/robustness of the results (further details are given in section 8.3).

8.4.2.3.3 Statistical Methods

Before any statistical analysis that assumes normally distributed observations, antibody titers will be $\log_{10}$-transformed. Individual titers below the limit of quantitation (LLQ) will be set to half that limit.

Geometric Mean Titers

The logarithmically (base 10) transformed antibody titers will be modeled using an analysis of covariance (ANCOVA) model with a qualitative factor for LHD153R adjuvant dosage (0 [for unadjuvanted MenC], 12.5, 25, 50 or 100 µg) and log (base 10) pre-vaccination titer as a covariate. The adjusted GMT and the two-sided, 95%, confidence intervals (CIs) of the GMT will be calculated based on this model as will the ratio of GMTs and corresponding CIs. The adjusted GMT and two-sided 95% CIs will be constructed by exponentiation (base 10) of the least square means of the logarithmically transformed (base 10) antibody titer. The ratio of GMTs (LHD153R adjuvant dosage minus MenC), and corresponding two-sided 95% CIs, will be constructed by exponentiation (base 10) of the least square differences obtained from this model. The model can be written as:

$$\log_{10}(y_{ik}) = \mu + \alpha_i + \beta x_{ik} + \varepsilon_{ik}$$

where μ represents a common overall mean, α_i represents the adjuvant dose group i effect, β represents the common slope for the log10 pre-vaccination titer, x_{ik} for subject k in adjuvant dose group I, and ε_{ik} represents random error for subject k in adjuvant dose group i.

Geometric Mean Ratios

The logarithmically (base 10) transformed within subject ratio of antibody titers (Day 29 / pre-vaccination) will be modeled using an analysis of variance model with a qualitative factor for LHD153R adjuvant dosage (0 [for non-LHD153R adjuvanted MenC], 12.5, 25, 50 or 100 µg). The adjusted GMR and the two-sided, 95% CIs of the GMR will be calculated based on this model. The model can be written as:

$$\log_{10}(y_{ik}) = \mu + \alpha_i + \varepsilon_{ik}$$

where μ represents a common overall mean, α_i represents the adjuvant dose group i effect and ε_{ik} represents random error for subject k in adjuvant dose group i.

Handling of missing values

For immunogenicity data, it may be reasonable to consider missing immunogenicity values as missing completely at random (MCAR), i.e., not informative. Therefore, the primary analysis will comprise a complete case analysis only, without introducing any bias. Imputation methods will not be used.

8.4.3 Analysis of Secondary Objective(s) 8.4.3.1

Analysis of Secondary Safety Objective(s) Not

applicable.

8.4.3.2 Analysis of Secondary Efficacy Objective(s)

Not applicable.

8.4.3.3 Analysis of Secondary Immunogenicity Objective(s)

8.4.3.3.1 Statistical Hypotheses

There are no statistical hypotheses associated with the secondary immunogenicity objectives. All analyses are descriptive.

8.4.3.3.2 Analysis Sets

The secondary immunogenicity analyses will be based on the PPS (further details are given in section 8.3) or the appropriate subset of subjects.

8.4.3.3.3 Statistical Methods

The secondary immunogenicity endpoints are:

- GMTs and corresponding GMRs measured by hSBA directed against MenC for samples collected at Day 8 and Day181.
- Percentage of subjects with hSBA seroresponse at Days 8, 29, and 181. seroresponse is defined as a post vaccination hSBA ≥8 for subjects with a baseline hSBA <4 or have an increase of at least 4 times the baseline hSBA level for subjects with prevaccination hSBA ≥4.
- Antibody geometric mean concentrations (GMCs) against MenC measured by ELISA for samples collected on Days 1 (baseline, prior to vaccination), 8, 29, and 181.
- The percentage of subjects with at least a 4-fold increase in antibody concentrations to MenC as measured by ELISA on Day 8, 29, and 181 relative to baseline (Day 1).

The GMTs for samples collected at Day 8 and Day 181 as well as the GMCs for samples collected at Day 1, Day 8, Day 29, and Day 181 will be analyzed using the same approach as for the primary immunogenicity endpoint.

The remaining immunogenicity endpoints are based on subjects meeting criteria for seroconversion or achieving a certain threshold value. These endpoints will be summarized using frequencies and percentages by LHD153R adjuvant dosage (0 [for non-LHD153R adjuvanted MenC], 12.5, 25, 50 or 100 µg). Two-sided 95% ClopperPearson CIs will also be provided for percentages. For analyses of seroconversion, separate summaries may be provided based on seropositivity status at baseline.

8.4.4 Analysis of Exploratory Objectives

Testing and analyses of exploratory endpoints may be performed after the Clinical Study Report (CSR) has been completed, in which case these data will be submitted as an addendum to the CSR.

In general, concentration and titer results will be summarized for each LHD153R adjuvant dosage group using geometric means and associated 2-sided 95% confidence intervals; and, categorical data will be summarized using frequencies and percentages, with corresponding two-sided, 95% confidence intervals.

8.5 Sample Size and Power Considerations of Primary Objectives

Sample size is not driven by statistical assumptions for formal hypothesis testing, but was based on the safety objective for the study. The table below provides the probability for various combinations of sample size (N) and presumed true frequency of a given event within an individual vaccine group

Frequency of Event	**Probability to Observe at Least 1 Subject with a Given Event For Various Choices of N**			
	4	**8**	**12**	**16**
0.05	0.1855	0.3366	0.4596	0.5599
0.10	0.3439	0.5695	0.7176	0.8147
0.15	0.4780	0.7275	0.8577	0.9257
0.20	0.5904	0.8322	0.9313	0.9718
0.30	0.8250	0.9423	0.9862	0.9967
0.40	0.8704	0.9832	0.9978	0.9997

The proposed combinations of sample sizes within each cohort are 4 aluminium hydroxide adjuvanted MenC-CRM$_{197}$ and 16 MenC-CRM$_{197}$ plus an assigned-level of LHD153R adsorbed to aluminium hydroxide. If all four cohorts are fully enrolled, there will be 16 subjects receiving aluminium hydroxide adjuvanted MenC-CRM$_{197}$.

With 16 subjects, events which occur at a frequency of 15% or more will be detected with at least 90% probability; and, events which occur at a frequency of 10% or more will be detected with 81% probability. With 4 subjects, events which occur at a frequency of 30% or more will be detected with at least 80% probability. Intermediate values of 8 and 12 are provided to correspond to sample sizes in the MenC- CRM$_{197}$ after cohort 2 and cohort 3 are fully enrolled.

8.6 Interim Analysis

The DMC will be reviewing the accumulating safety data from the study in order to continue enrollment of subjects within a cohort and whether to enroll subjects into the next cohort.

In addition to these periodic reviews, there will be a safety and immunogenicity interim analysis for the selection of an LHD153R adjuvant dosage based on the data collected through Day 29 from subjects enrolled in all cohorts. This analysis will be performed by personnel not involved in study decisions. The results will be unblinded at the group level thereby preserving the blind for individual subjects. No adjustment to the overall alpha will be performed as the data collected subsequent to this analysis involve secondary and exploratory endpoints.

9.0 SOURCE DOCUMENTATION, STUDY MONITORING AND AUDITING

Study monitoring and auditing will be standardized and performed in accordance with the Sponsor's or delegated contract research organization's (CRO) standard operating procedures and applicable regulatory requirements (e.g., FDA, EMA, and ICH guidelines).

Prior to enrolment of the first study subject, GSK or delegate will train investigators and/or their study staff on the study protocol, all applicable study procedures, documentation practices and all electronic systems. CRFs must be completed for each enrolled subject (see section 8.3.1 for definition of enrolled subject). Documentation of screened but not enrolled subjects must be maintained at the site and made available for review by the site monitor.

9.1 Source Documentation

Prior to the start of the study, the site staff participating in the study conduct will be instructed on what documents will be required for review as source documents. The kinds of documents that will serve as source documents will be agreed between Sponsor or delegate and investigator and designees and specified in the SDA/Source Data Verification Form prior to subject enrolment.

In addition, source documentation **must** include all of the following: subject identification (on each page), eligibility and participation, proper informed consent procedures, dates of visits, adherence to protocol procedures, adequate reporting and follow-up of adverse events, documentation of prior/concomitant medication/vaccines, study vaccine receipt/dispensing/return records, study vaccine administration information, any data collected by a telephone conversation with the subject and date of completion and reason.

The subject must also allow access to the subject's medical records. Each subject must be informed of this prior to the start of the study and consent for access to medical records may be required in accordance with local regulations.

All safety data reported by subjects must be written down in source documents. If there are multiple sources of information (e.g., Subject Diary, verbal report of the subject, telephone contact details, medical chart) supporting the diagnosis of an adverse event, these sources must be identified in the source documents, discrepancies between sources clarified, the ultimate diagnosis must be justified and written in the source documents, and this diagnosis must be captured in the appropriate CRF page. The CRF must also

capture which source(s) of information were used to determine the adverse event (e.g., subject recall, medical chart, Subject Diary).

9.2 Study Monitoring, Auditing and Source Data Verification

Prior to enrolment of the first study subject, GSK or its designee (e.g., a CRO) will develop a Monitoring Plan to specify how centralized and/or on-site monitoring, including clinical specimens reconciliation, will be performed for the study. Study progress will be monitored as frequently as necessary to ensure:

- that the rights and well-being of human subjects are protected,
- the reported study data are accurate, complete, and verifiable from the source documents and
- the conduct of the study is in compliance with the current approved protocol/amendment(s), GCP and applicable regulatory requirements.

Contact details for the team involved in study monitoring will be provided to the investigator. Study data recorded on CRFs will be verified by checking the CRF entries against source documents in order to ensure data completeness and accuracy as required by study protocol.

Additional documents such as the investigator site file, pharmacy records, and informed consent documentation must also be available for review if requested. Arrangements for monitoring visits will be made in advance in accordance with the monitoring plan, except in case of emergency.

The investigator and/or site staff must make source documents of subjects enrolled in this study available for inspection at the time of each monitoring visit and Sponsor audits, when applicable. These documents must also be available for inspection, verification and copying, as required by regulations, by officials of the regulatory health authorities (e.g., FDA, EMA and others) and/or ECs/IRBs. The investigator and study site staff must comply with applicable privacy, data protection and medical confidentiality laws for use and disclosure of information related to the study and enrolled subjects.

10.0 DATA MANAGEMENT

10.1 Data Entry and Management

In this study, all clinical data (including, but not limited to, AE/SAEs, concomitant medications, medical history, and physical assessments), safety data, and immunogenicity data will be entered into an EDC system, which is compliant with Title 21 Part 11

policies of the Code of Federal Regulations (FDA, 1997). The data system includes password protection and internal quality checks. The EDC system will be designed and validated by the Sponsor prior to activation for data entry by sites. The investigator or designated delegate must review data entered and electronically sign the CRFs to verify their accuracy.

Access to the EDC system for data entry or review will require training and distinct individual access code assignments to those site staff members who will be entering study data and those involved in study oversight who may review study data. Data are collected within the EDC system, to which the Sponsor and site monitors have exclusively "read only" access.

Paper CRFs will be provided for each pregnant subject by the Sponsor. All appropriate pregnant subject data collected will be recorded on this form. One copy must be retained by the investigator, and all other copies (including the original copy) will be returned as directed by the Sponsor. Instructions on how to complete this form will be provided to the investigator.

10.2 Data Clarification

As part of the conduct of the trial, the Sponsor may have questions about the data entered by the site, referred to as queries. The monitors and the Sponsor are the only parties that can generate a query. All corrections and clarifications will be entered into the EDC system and will be identified by the person entering the information, the reason for the change, as well as the time of the changes made. If changes are made to a previously and electronically signed CRF, the investigator must confirm and endorse the changes

10.3 Data Protection

GSK respects the subjects' rights to privacy and will ensure the confidentiality of their medical information in accordance with all applicable laws and regulations.

The Sponsor as Data Controller according to the European Directive on the protection of individuals with regard to the processing of personal data and on the free movement of such data (95/46/EC) confirms herewith compliance to Directive 95/46/EC in all stages of Data Management.

11.0 RECORD RETENTION

Investigators must retain all study records required by GSK and by the applicable regulations in a secure and safe facility. The investigator must consult a GSK representative before disposal of any study records, and must notify the Sponsor of any change in the location, disposition, or custody of the study files. Essential documents must be retained for 15 years. “Essential documents” are defined as documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. These documents should be retained for a longer period, however, if required by the applicable national regulatory or institutional requirements.

These principles of record retention will also be applied to the storage of laboratory samples, provided that the integrity of the stored sample permits testing.

12.0 USE OF INFORMATION AND PUBLICATION

GSK assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov, and in compliance with current regulations.

GSK also assures that key results of this clinical study will be posted in a publicly accessible database within the required time-frame from the End of Study as defined in section 3.9.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

GSK must be notified of any intent to publish data collected from the study and prior approval from GSK must be obtained prior to submission for publication.

13.0 ETHICS

13.1 Regulatory and Ethical Compliance

The study will be conducted in compliance with the protocol, GCP and applicable regulatory requirement(s).

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, European Directive 2001/20/EC, GSK codes on protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki (European Council 2001, US Code of Federal Regulations, ICH 1997).

13.2 Informed Consent Procedures

Eligible subjects may only be included in the study after providing written informed consent or assent, as described in section 5.1.1. Before the start of the study, the investigator will have the informed consent and any other materials that will be provided to the subjects reviewed and approved by the IRB/EC. This review and approval will be documented and stored with other study documents. The investigator or designee must fully inform the subject or legal guardian of all pertinent aspects of the study. A copy of the written informed consent will be given to the subject or the designee. The subject/designee must be allowed ample time to ask about the details of the study and to make a decision as to whether or not to participate in the study. The subject and/or legal guardian(s) **must** sign the consent form indicating their agreement to participate in the study before any study-related procedures are conducted. The informed consent process may be conducted up to 28 days prior to vaccination on Day 1. If the subject is unable to read and write, a witness must be present during the informed consent discussion and at the time of informed consent signature.

Prior to the start of the study, GSK will provide to investigators a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by GSK before submission to the IRB/EC and a copy of the approved version must be provided to GSK after IRB/EC approval.

Women of childbearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements indicated in the protocol for the duration of the study. In case of doubt on

the ability of a subject to adhere to these requirements, that subject should not be allowed in the study

13.3 Responsibilities of the Investigator and IRB/EC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB/EC before study start. Properly constituted IRB/EC is defined in ICH Guideline for Good Clinical Practice E6 (R1), Section 3 (ICH, 1997). A signed and dated statement that the protocol and informed consent have been approved by the IRB/EC must be given to GSK before study initiation. Prior to study start and at any time the protocol is amended during study conduct, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to GSK monitors, auditors, GSK Clinical Quality Assurance representatives, designated agents of GSK, IRBs/ECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform GSK immediately that this request has been made.

The investigator also responsible for the following:

- Maintaining a list of appropriately qualified persons to whom the investigator has delegated significant study-related duties.
- Demonstrating the capability of recruiting the required number of suitable subjects within the recruitment period.
- Demonstrating sufficient time and staffing to properly conduct and complete the study within the agreed study period.
- Ensuring that all persons assisting with the study are adequately informed about the protocol, the investigational product(s), and their study-related duties and functions
- Ensuring that appropriately trained health care professionals are responsible for all study-related medical decisions and for ensuring appropriate medical care of subjects experiencing any adverse event related to the study.
- If permission to do so is given by the subject, ensuring that the subject's primary healthcare provider is informed of the subject's participation in the study.

The investigator should not implement any deviation from, or changes of the protocol without agreement by the Sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone

number(s)). In addition, the investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to study subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

(a) to the IRB/IEC for review and approval/favourable opinion,

(b) to the Sponsor for agreement and, if required,

(c) to the regulatory authority(ies).

13.4 Protocol Amendments

An amendment is a written description of change(s) to or formal clarification of a study protocol which may impact on the conduct of the clinical study, potential benefit of the clinical study, or may affect subject safety, including changes of study objectives, study design, subject population, sample sizes, study procedures, or significant administrative aspects. An administrative change of a study protocol is a minor correction or clarification that has no significant impact on the way the clinical study is to be conducted and no effect on subject safety (e.g., change of telephone number(s), logistical changes). Protocol amendments must be approved by GSK, health authorities where required, and the IRB/EC. In cases when the amendment is required in order to protect the subject safety, the amendment can be implemented prior to IRB/EC approval. Notwithstanding, the need for formal approval of a protocol amendment, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, GSK should be notified of this action, the IRB/EC at the study site, and, if required by local regulations, the relevant health authority should be informed within 10 working days.

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APPENDIX A: GRADING SCALES FOR SOLICITED LOCAL ADVERSE EVENTS*

(Adapted from CBER 2007b)

Adverse event Following Administration of Injectable Product	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Pain	present but does not interfere with activity	interferes with activity	prevents daily activity
Induration / Swelling / Erythema	25 – 50 mm	51 – 100 mm	> 100 mm

*This toxicity grading scale is adapted from CBER 2007 to enable ease of reporting by Subjects in the source documents for 'patient reported' solicited adverse events.. 'Grade 4' is not listed here but will be defined in the Statistical Analysis Plan as necessary.

APPENDIX B: GRADING SCALES FOR SOLICITED SYSTEMIC ADVERSE EVENTS*

(Adapted from CBER 2007b)

Systemic Adverse event		Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Fever	**°C**	38.0 – 38.4	38.5 – 38.9	39.0 – 40
	°F	100.4 – 101.1	101.2 - 102	102.1 - 104
Chills		present but does not interfere with activity	interferes with activity	prevents daily activity
Loss of Appetite		Loss of appetite without decreased oral intake	decreased oral intake without weight loss	decreased oral intake with weight loss
Nausea		Nausea present but not interfering with oral intake	Nausea leading to decreased oral intake	Nausea leading to minimal to no oral intake
Vomiting		1-2 episodes/24 hours	>2 episodes/24 hours	requires outpatient hydratation
Diarrhea		2-3 loose stools /24 hours	4-5 loose stools /24 hours	6 or more watery stools /24 hours or requires outpatient IV hydration
Generalized Myalgia		present but does not interfere with activity	interferes with activity	prevents daily activity
Generalized Arthralgia		present but does not interfere with activity	interferes with activity	prevents daily activity
Headache		present but does not interfere with activity	interferes with activity	prevents daily activity
Fatigue		present but does not interfere with activity	interferes with activity	prevents daily activity
Generalized Rash		localized area of the skin (1 extremity only)	moderate area of the skin (2 or more body regions without whole body involvement)	most of the skin
Urticaria		localized area of the skin (1 extremity only)	moderate area of the skin (2 or more body regions without whole body involvement)	most of the skin

*This toxicity grading scale is adapted from CBER 2007b to enable ease of reporting by Subjects in the source documents for 'patient reported' solicited adverse events. 'Grade 4' is not listed here but will be defined in the statistical analysis plan as necessary

APPENDIX C: TOXICITY SCALES FOR LABORATORY ABNORMALITIES (SERUM CLINICAL CHEMISTRY)

Serum*,**	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)***
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN

*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

**Laboratory values that fall in the normal range may be assigned a category of "Grade 0."

TOXICITY SCALES FOR LABORATORY ABNORMALITIES

***The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value. "ULN" = the upper limit of the normal range.

APPENDIX D:

(HEMATOLOGY)

Hematology*,*	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000

TOXICITY SCALES FOR LABORATORY ABNORMALITIES

Platelets Decreased cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000

*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
**Laboratory values that fall in the normal range may be assigned a category of "Grade 0."

APPENDIX E:

(URINE)

Urine*,**	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
**Laboratory values that fall in the normal range may be assigned a category of "Grade 0."

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CLINICAL STUDY PROTOCOL SPONSOR SIGNATURE PAGE

Study Number: V132_01EXP

Protocol Title: A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine in Healthy Adults (18-45 years of age)

Date of Final Issued Protocol and Version: 11 SEP 2015, Version 5

Signature page for sponsor's representative

The following sponsor's representative has reviewed and approved the protocol entitled "A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine in Healthy Adults (18-45 years of age)." In addition, this study protocol has been approved by the GSK Protocol Review Committee and received an electronic approval signature on 11 SEP 2015.

[redacted] 21/SEP/15

Cluster Physician, GSK Date, DD MMM YY

[redacted]

Printed Name of Cluster Physician, GSK

PPD	PP D

CLINICAL STUDY PROTOCOL AMENDMENT

Study Number: V132_01EXP

Protocol Title: A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine in Healthy Adults (18-45 years of age)

Amendment Number 5

Revised Protocol version 6.0 issued on 19 Jan 2016

The present amendment reflects changes to the Protocol version 5.0 issued on 11SEP15

DESCRIPTION OF CHANGE(S) AND RATIONALE:

CHANGE	LOCATION(S) OF CHANGE	RATIONALE FOR CHANGE
Added under pausing guidelines that in case criteria for pausing are met, vaccination will be suspended and a full safety review by the DMC and EC/IRB will be performed.	Section 3.6 'Stopping/Pausing Guidelines' (page 38-39)	The Ethics Committee approval was received under the condition that the Ethics Committee is consulted in case pausing criteria are met.
Added that the names of the independent DMC members are mentioned in the DMC charter	Section 3.7 'Data Monitoring Committee' (page 39)	Ethics Committee provided comment that members of the DMC should be mentioned and be independent
Added Appendix F with grading scales for Vital Signs.	Appendix F (page 105)	For clarification of the grading scales for vital signs
Added description of the procedure for emergency unblinding.	Section 3.3 'Blinding Procedures' (page 33-34)	The Paul-Ehrlich Institute requested to describe the procedure for emergency unblinding.

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CLINICAL STUDY PROTOCOL V132_01EXP Version 6

A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine in Healthy Adults (18-45 years of age)

EUDRACT No. 2014-002430-31

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PROTOCOL SYNOPSIS V132_01EXP

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
GlaxoSmithKline Biologicals S.A.	V132_01EXP	MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and Meningococcal C-CRM$_{197}$ Conjugate Vaccine
Title of Study: A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine in Healthy Adults (18-45 years of age)		
Study Period: Approximately 12 months for each subject		**Clinical Phase:** Phase 1

Background and Rationale:

Neisseria meningitidis (*N. meningitides*)serogroup C (MenC) is one of the major serogroups causing invasive meningococcocal disease. Case fatality in Germany has ranged between 6% and 8% between 1999 and 2006, and has remained generally consistent across the different European countries, varying between 6-11%, with the case fatality rate being notably higher for serogroup C disease than for serogroup B. The safety and immunogenicity of the GSK Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) has been confirmed through years of commercial use. For children over the age of 12 months, for adolescents and for adults a single dose is recommended. For infants between 2 and 12 months of age, the recommended schedule for primary immunization with the Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) is two doses given with an interval of at least 2 months A more potent Meningococcal CCRM$_{197}$ Conjugate Vaccine formulation might enable a reduction of the antigen dosage and/or a reduction in the number of doses needed in infants. One approach to achieve more potent well-characterized sub-unit vaccines - like the Meningococcal C-CRM$_{197}$ Conjugate Vaccine - is the use of new adjuvants that activate the Toll-like receptor (TLR) pathway.

GSK is developing a small molecule immune potentiator (SMIP) LHD153 that is an agonist for TLR7. The objective driving the development of LHD153 is to achieve a vaccine adjuvant with strong immunopotentiating properties and minimal side effects. In line with this objective, it has been postulated that the ideal SMIP should remain local

and target innate immune cells at the injection site. To this end, LHD153 contains a functional phosphonate group to allow for adsorption to aluminium hydroxide. The

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arginine salt derivative of this compound is LHD153R. Preclinical results from animal models for bacterial and viral antigens, including MenC, MenB, rabies, HIV and respiratory syncytial virus (RSV) showed increased functional antibodies and antigenspecific T-cells with LHD153R adsorbed to aluminium hydroxide (Aluminium Hydroxide/LHD153R) when compared to aluminium hydroxide adjuvanted controls. *In vitro* toxicity screens confirmed that LHD153R is not phototoxic, genotoxic or mutagenic. Furthermore, toxicology studies in dog and rats showed that intramuscular (IM) injection of Aluminium Hydroxide/LHD153R was well tolerated. Importantly, in contrast to free LHD153R, toxicokinetic analysis in rats and dogs confirmed very limited exposure of LHD153 when LHD153R was adsorbed to aluminium hydroxide after IM injection.

The aim of this Phase 1 clinical study is to assess the safety of Aluminium Hydroxide/LHD153R adjuvanted MenC-CRM_{197} conjugate vaccine (MenCCRM$_{197}$/Aluminium Hydroxide/LHD153R) and to compare the antibody-mediated immune response elicited by MenC-CRM_{197}/Aluminium Hydroxide/LHD153R with the licensed aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (Menjugate®). Furthermore, a comprehensive set of exploratory objectives has been selected to assess the systemic exposure of LHD153 after intramuscular injection of MenC-CRM_{197}/Aluminium Hydroxide/LHD153R, to evaluate the quality of the specific immune response against MenC-CRM_{197} in detail and to evaluate biomarkers that may be predictive of safety and/or innate immune activation.

The licensed Meningococcal C-CRM_{197} Conjugate Vaccine (Menjugate®) has been selected as the primary vaccine candidate to assess the safety and immunopotentiating properties of Aluminium Hydroxide/LHD153R for several reasons. Firstly, the safety and immunogenicity profiles of the Meningococcal C-CRM_{197} Conjugate Vaccine (Menjugate®) have been well established through years of commercial use. Secondly, a more potent MenC-CRM_{197} conjugate vaccine might enable a reduction of the antigen dosage or the number of doses needed in infants. Finally, MenC-CRM_{197} is a wellcharacterized, single conjugate antigen preparation which provides an ideal setting to evaluate the potential of this new Aluminium Hydroxide/LHD153R adjuvant.

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Study Objectives:

Primary Safety Objective:

To assess the safety of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R as compared to that of aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine.

Primary Immunogenicity Objective:

To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine at Day 29, as measured by human complement serum bactericidal assay (hSBA) directed against MenC.

Secondary Immunogenicity Objectives:

1. To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal CCRM$_{197}$ Conjugate Vaccine, at Day 8 and Day 181 after vaccination, as measured by hSBA directed against MenC. Baseline antibody titers will also be measured by hSBA.
2. To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal CCRM$_{197}$ Conjugate Vaccine at Day 8, Day 29 and Day 181 after vaccination, as measured by an enzyme-linked immunosorbent assay (ELISA) to MenC. Baseline antibody concentrations will also be measured by ELISA.

Exploratory Objectives:

1. To evaluate the systemic exposure of LHD153 at several early time-points after IM injection of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R or aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine.
2. To explore the frequency of B cells specific for MenC polysaccharide and CRM$_{197}$ protein at baseline (Day 1) and at Day 8, Day 29 and Day 181 after vaccination with

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MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R or the aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine. Subsequently, the B cell repertoire of the antigen specific B cells will be analyzed in a selected subset of subjects.

3. To explore the baseline T cell mediated immunity to CRM$_{197}$ and to evaluate the frequency and quality of CRM$_{197}$ specific T cells induced by MenC-CRM$_{197}$/Aluminium Hydroxide/ LHD153R compared to aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine at Day 8 and Day 29.
4. To evaluate biomarkers that may be predictive for safety and/or innate immune activation.

Study Design:

This Phase 1, randomized, observer-blind, dosage-escalation study will be performed at a single center. In total, approximately 80 healthy male and healthy non-pregnant female adults (18-45 years of age) will be enrolled in the study. Subjects will be randomized to receive a single IM vaccination of either the licensed aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (i.e. 10 µg MenC conjugated to CRM_{197}, adjuvanted with 1 mg aluminium hydroxide) or one of four dosages of the investigational vaccine, MenC-CRM_{197}/Aluminium Hydroxide/LHD153R (i.e. 10 µg MenC conjugated to CRM_{197}, adjuvanted with 1 mg aluminium hydroxide and one of four dosages [12.5, 25, 50 or 100 µg] of LHD153R).

For the dosage-escalation of LHD153R, the subjects will be enrolled into 1 of 4 cohorts, in a stepwise manner with 20 subjects per cohort. Subjects in all cohorts will be randomized in a 1:4 ratio, to receive either aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (control) or MenC-CRM_{197}/Aluminium Hydroxide/LHD153R with increasing doses of LHD153R.Cohort 1 will receive 12.5 µg of LHD153R; Cohort 2 will receive 25 µg of LHD153R; Cohort 3 will receive 50 µg of LHD 153; and Cohort 4 will receive 100 µg of LHD153R (Table 1).

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Table 1: Subjects Randomized per Cohort and Treatment Dosage Group

Cohort	Group	Subjects/ Group	MenC Dosage* (µg)	Adjuvant Dosages		Total Volume/Dose	Total Subjects/Cohort
				Aluminium Hydroxide (mg)	LHD153R (µg)		
1	A	4	10	1	0	0.5 mL	20
	B	16	10	1	12.5	0.5 mL	
2	A	4	10	1	0	0.5 mL	20
	C	16	10	1	25	0.5 mL	
3	A	4	10	1	0	0.5 mL	20
	D	16	10	1	50	0.5 mL	
4	A	4	10	1	0	0.5 mL	20
	E	16	10	1	100	0.5 mL	

*Conjugated to 12.5-25 µg CRM_{197}

After vaccination, all subjects will be confined to the clinical site for 24 hours for clinical observation, including but not limited to observations for solicited and unsolicited adverse events, body temperature measurements and blood sampling for exploratory endpoint measurements.

Importantly, all cohorts will have a staggered entry based on Data Monitoring Committee (DMC) reviews.

- For each cohort, the first 5 subjects (i.e. the first 1:4 randomization block) to receive either aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (n=1) or MenC-CRM_{197}/Aluminium Hydroxide/LHD153R (n=4) will be treated at a vaccination rate of 1 subject each day.
- After entry of the first 5 subjects in each cohort, the enrollment will be paused. The remaining 15 subjects for each cohort will be enrolled only after DMC review of the safety results obtained through Day 14 has been finalized (Table 2).
- In addition, enrollment of the first 5 subjects in the next cohort will only proceed after the Day 14 safety results of the first 5 subjects of the previous cohort have been reviewed by the DMC (Table 2).
- Furthermore, all available Day 14 and Day 29 safety results will be included in DMC reviews between the different enrollment stages.

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Table 2: Overview of staggered entry of subjects based on DMC reviews

Stage	Dosage Cohort	MenC-CRM$_{197}$/ Aluminium Hydroxide (n)	MenC-CRM$_{197}$/ Aluminium Hydroxide /LHD153R (n)
1	1	1	4
Enrollment pause until DMC review of Stage 1 Day 14 Safety Results			
2	1	3	12
	2	1	4
Enrollment pause until DMC review of Stage 1 Day 29 and Stage 2 Day 14 Safety Results			
3	2	3	12
	3	1	4
Enrollment pause until DMC review of Stage 2 Day 29 and Stage 3 Day 14 Safety Results			
4	3	3	12
	4	1	4
Enrollment pause until DMC review of Stage 3 Day 29 and Stage 4 Day 14 Safety Results			
5	4	3	12

The DMC review will be performed according to predefined stopping/pausing guidelines used to ensure the safety of study subjects. These stopping/pausing guidelines are based on FDA guidance and with grading scales from the CBER Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials". See protocol section 3.6 for further details.

Safety Measurements

Schedule of safety data collection:

- Solicited local and systemic adverse events (AEs), body temperature and all unsolicited AEs will be collected until Day 14.
- All serious adverse events (SAEs), medically attended AEs, AEs leading to study withdrawal, new onset of chronic disease (NOCDs), and adverse events of special interest (AESIs) will be collected from the date of signed informed consent to study completion at Day 366.
- All concomitant medications administered in relation to the reported AEs will be

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collected from vaccination to study completion at Day 366.

Solicited local AEs include injection site erythema, injection site induration, injection site pain and injection site swelling. Solicited systemic AEs include body temperature ≥ 38.0°C (as measured orally), loss of appetite, nausea, fatigue, generalized myalgia, generalized arthralgia, headache, chills, vomiting, diarrhea, generalized rash and urticaria.

All AESIs will be reported in the same manner as SAEs. All AEs will be monitored until resolution or, if the AE becomes chronic, a cause is identified. If an AE is unresolved at the conclusion of the study, a clinical assessment will be made by the investigator and the medical monitor to determine whether or not continued follow-up of the AE is warranted.

The relationship of the study treatment to any AE will be determined by the investigator as probably related, possibly related, or not related; the relationship of the study treatment to any SAE will be determined by the investigator as probably related/suspected, or not related.

Safety Laboratory Parameters

To assess laboratory AEs, blood and urine samples will be collected from each subject as outlined in Table 3 to perform blood chemistry, hematology, and urine analyses.

Safety laboratory samples will be drawn from all subjects at pre-vaccination screening (between Day -28 and Day -3) at Day 1 (pre-vaccination and 24h after vaccination), at Day 8 and at Day 29. Safety laboratory assessments will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, liver function tests (ALT, AST), a complete blood count and C-reactive protein. A urine sample will be collected at the same time-points and will be assessed for the presence of protein, glucose and red blood cells.

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Primary and Secondary Immunogenicity Measurements

Four blood samples per subject (i.e. at Day 1, Day 8, Day 29 and Day 181) will be collected for serum preparation and determination of antibody-mediated immune responses to MenC-CRM$_{197}$ as outlined in Table 3 and Table 4. See section 7.3 for further details.

Exploratory Measurements

In all subjects who agree by signing a separate Informed Consent, additional blood samples will be collected at Day 1, Day 4, Day 8, Day 29 and Day 181 for exploratory assays as outlined in Table 3 and Table 4. The purpose of these assays is to assess the systemic exposure of LHD153, to determine the frequency and quality of B- and T-cells specific for MenC polysaccharide and/or CRM$_{197}$ and to evaluate biomarkers that may be predictive of safety and/or innate immune activation. Subsequently, MenC-CRM$_{197}$ specific B-cell repertoires will be analyzed in a selected subset of subjects, dependent on the results from primary and secondary immunogenicity measurements and the volume of blood remaining for additional testing. See section 7.4 for further details. All exploratory analyses may be performed after the Clinical Study Report (CSR) has been completed, in which case these data will be submitted as an addendum to the CSR.

Number of Subjects planned:

Approximately 80 adult subjects will be randomized, with anticipated dropout rates of 5% by Day 181 (last serology time point), and 10%, by Day 366 (last safety time point).

Sample size is not driven by statistical assumptions for formal hypothesis testing, but the proposed number of subjects will be sufficient to provide a descriptive summary of the safety and immunogenicity of the study vaccine.

Study Population and Subject Characteristics:

Healthy adult male and female volunteers between 18-45 years of age, inclusive.

The list of inclusion and exclusion criteria is included in protocol section 4.0.

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Study Vaccines:

The MenC-CRM$_{197}$ conjugate is a lyophilized powder consisting of 10 µg of MenC polysaccharide conjugated to 12.5-25 µg CRM$_{197}$ carrier protein. The MenC-CRM$_{197}$ lyophilized powder will be reconstituted with adjuvant by the unblinded designated site staff member who is to follow the procedure as described in the vaccine preparation instructions in the Investigator Site File (i.e. the vaccine will be prepared in the clinic prior to administration).

The lyophilized MenC-CRM$_{197}$ powder will be reconstituted with either:

(a) aluminium hydroxide adjuvant

(b) Aluminium Hydroxide/LHD153R adjuvant with specified dosages of LHD153R (12.5, 25, 50 or 100 µg)

The components for each formulation of MenC-CRM$_{197}$ will be provided in a separate kit.

Aluminium Hydroxide/LHD153R with specified dosages of LHD153R will be prepared by dilution of the highest Aluminium Hydroxide/LHD153R dosage (100 µg of LHD153R) with aluminium hydroxide.

In each cohort, subjects will be randomized to receive one injection of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R adjuvant or aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine. The 0.5 mL of vaccine will be injected IM in the deltoid muscle, with preference that the injection is administered in the nondominant arm.

Primary Safety Endpoint:

Safety will be assessed by measuring the frequency of local and systemic solicited AEs, unsolicited AEs, SAEs, AESIs, NOCDs, and safety laboratory data for all subjects. Specifically,

- The frequency and percentage of subjects with solicited local and systemic AEs through Day 14. Time intervals after vaccination that will be summarized are: 30

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min post-vaccination, Days 1-4 (without 30 min), Days 5-8, Days 8-14, Days 1-8 (without 30 min) and Days 1-14 (without 30 min).

- The frequency and percentage of subjects with any unsolicited AEs from the day of vaccination (Day 1) to Day 14.
- The frequency and percentage of subjects with SAEs, medically attended AEs, AEs leading to study withdrawal, NOCDs, AESIs for the following time periods: day of signed informed consent until study completion (Day 366), day of vaccination (Day 1) to Day 29 and Day 29 to study completion (Day 366).
- The absolute values and changes in hematology, chemistry, and urinalysis parameters.
- The frequency and percentage of subjects with abnormal laboratory parameter values as classified by investigator normal ranges (low, normal, high) and as classified by CBER toxicity grading scales, when available.

Primary Immunogenicity Endpoint:

Geometric mean titers (GMTs) measured by hSBA directed against MenC from samples collected on Day 1 (baseline, before vaccination) and Day 29 as well as the GMR of the titers (Day 29 / Day 1).

Secondary Immunogenicity Endpoints:

- GMTs and corresponding GMRs measured by hSBA directed against MenC for samples collected at Day 8 and Day181.
- Percentage of subjects with hSBA seroresponse at Day 8, Day 29, and Day 181. seroresponse is defined as a post vaccination hSBA $\geq$8 for subjects with a baseline hSBA <4 or have an increase of at least 4 times the baseline hSBA level for subjects with pre-vaccination hSBA $\geq$4.
- Antibody geometric mean concentrations (GMCs) against MenC measured by ELISA for samples collected on Day 1 (baseline, prior to vaccination), Day 8, Day 29, and Day 181.
- The percentage of subjects with at least a 4-fold increase in antibody concentrations

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
GlaxoSmithKline Biologicals S.A.	V132_01EXP	MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and Meningococcal C-CRM$_{197}$ Conjugate Vaccine

to MenC measured by ELISA on Day 8, Day 29, and Day 181 relative to baseline (Day 1).

Exploratory Endpoints:

Testing and analyses of exploratory endpoints may be performed after the Clinical Study Report (CSR) has been completed, in which case these data will be submitted as an addendum to the CSR.

1. Serum concentration of LHD153 at Day 1 baseline (prior to vaccination), Day 1 (1h , 2h, 4h, 8h, and 24h after vaccination) and Day 4 by LC-MS/MS.
2. Frequency of MenC polysaccharide-specific and CRM$_{197}$-specific B cells at Day 1 (baseline), Day 8, Day 29, and Day 181 by ELISPOT.
3. Diversity of the MenC polysaccharide-specific B-cell repertoire at Day 1 (baseline), Day 8, Day 29, and Day 181 by immunoglobulin cDNA sequencing.
4. Frequency and quality of T cells specific for CRM$_{197}$ at Day 1 (baseline), Day 8, and Day 29 by flow cytometry using intracellular staining with a panel of cytokines and staining of surface markers to identify cell populations.
5. Serum concentrations of a panel of 30 chemokines and cytokines at Day 1 baseline (prior to vaccination), Day 1 (6h and 24h after vaccination), Day 4, and Day 8 by electrochemo-luminescence based assay.
6. Gene expression profile in whole blood at Day 1 baseline (prior to vaccination), Day 1 (6h and 24h after vaccination), Day 4, and Day 8 by RNA micro array analysis.
7. Number and activation status of myeloid and lymphoid cell populations at Day 1 baseline (prior to vaccination), Day 1 (24h after vaccination), Day 4 and Day 8 by flow cytometry.

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
GlaxoSmithKline Biologicals S.A.	V132_01EXP	MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and Meningococcal C-CRM$_{197}$ Conjugate Vaccine

Statistical Analyses:

The study is exploratory in nature, thus analyses will be descriptive and no formal hypothesis testing will be performed. Primary Safety Analyses

The primary safety analyses will be based on the safety set for solicited and unsolicited adverse events. There is no statistical null hypothesis associated with the safety objective, which will be analyzed descriptively.

Immunogenicity Analyses

The primary immunogenicity analyses will be based on the per-protocol set (PPS) on Day 29. The primary analyses will also be performed using the Full Analysis Set (FAS) as a measure of the sensitivity/robustness of the results. All other immunogenicity assessments will be performed using the PPS or the appropriate subset of subjects. The antibody concentrations/titers will be summarized using GMC/GMTs and two-sided 95% confidence intervals (CIs) constructed by exponentiation (base 10) of the least square means of the logarithmically transformed (base 10) antibody titer. The 95% CIs will be obtained from an analysis of covariance (ANCOVA) with baseline concentration/titer as a covariate. Additional details will be further described in the Statistical Analysis Plan.

The immunogenicity endpoints based on subjects meeting criteria for seroconversion or achieving a certain threshold value will be summarized using frequencies and percentages and associated two-sided 95% Clopper-Pearson CIs. For analyses of seroconversion, separate summaries may be provided based on seropositivity status at baseline.

Interim Analysis:

An Interim Analysis will be performed on the immunogenicity and safety data collected from all subjects until Day 29, after all cohorts have been enrolled. Further details regarding the interim analysis are contained in section 8.6.

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
GlaxoSmithKline Biologicals S.A.	V132_01EXP	MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and Meningococcal C-CRM$_{197}$ Conjugate Vaccine

Data Monitoring Committee:

An independent DMC will be implemented to review safety data during scheduled periodic reviews. The DMC will review safety data collected until Day 14, as described in the DMC charter and in the Statistical Analysis Plan, after enrollment of the first 5 subjects in each cohort, before proceeding with enrollment of the remaining 15 subjects in each cohort. In addition, enrollment of the first 5 subjects of the next cohort will only proceed after the Day 14 safety results of the first 5 subjects of the previous cohort have been reviewed. Furthermore, all available Day 14 and Day 29 safety results will be included in DMC reviews between the different enrollment stages. Further information regarding the DMC is discussed in more detail in the protocol, section 3.7.

Table 3: Time and Events Table – Treatment Period (until Day 29)

	Visit Type	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit	Phone Call	Clinic Visit
	Study Day	**-28 to -3**	**1**	**4**	**8**	**15**	**22**	**29**
	Visit Window (Days)	**n/a**	**n/a**	**n/a**	**-1/+1**	**+1**	**n/a**	**-2/+2**
	Visit Number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**
Study Event	**References**							
Study Treatment								
Vaccination	Section 5.2		X					
Screening and Safety								
Informed Consent	Section 5.1.1	X						
Demographic Data & Medical History	Sections 5.1.2	X						
Physical Exam	Sections 5.1.2 and 5.2.1	X	X[a]					
Safety Laboratory blood draw (10 ml)	Section 7.1.7	X	X[b]		X			X
Urinalysis	Sections 7.1.7	X	X[b]		X			X
Pregnancy Test	Sections 5.1.2 and 5.2.1	X	X[a]					
Exclusion/Inclusion Criteria	Section 4.0	X	X[a]					
Randomization	Section 5.2.3		X[a]					
30 min and 24 hr Post Injection Assessment	Section 5.2.5		X[c]					
Subject Diary Dispensed with Training	Section 5.2.5		X					
Subject Diary Reminder	Section 5.2.5			X	X			

Subject Diary Reviewed and Collected	Section 5.3.1					X		
Assess all solicited AEs	Section 7.1.1 and 7.1.3					X		
Assess all unsolicited AEs	Sections 7.1.2 and 7.1.3	X	X	X	X	X		

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	Visit Type	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Phone Call**	**Clinic Visit**
	Study Day	**-28 to -3**	**1**	**4**	**8**	**15**	**22**	**29**
	Visit Window (Days)	**n/a**	**n/a**	**n/a**	**-1/+1**	**+1**	**n/a**	**-2/+2**
	Visit Number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**
Study Event	**References**							
Assess SAEs	Section 7.1.4	X	X	X	X	X	X	X
Assess AESIs	Section 7.1.4.1	X	X	X	X	X	X	X
Assess NOCDs, medically attended AEs, AEs leading to withdrawal	Sections 7.1.3	X	X	X	X	X	X	X
Assess relevant medications	Sections 5.1.2 and 6.5	X	X	X	X	X	X	X
Blood draws for Immunogenicity and Exploratory Objectives								
Serum Blood Draws (Primary/Secondary Objectives; 10 mL)	Section 3.5		X_a		X			X
Serum Blood Draws (Exploratory Objectives; 5 mL)	Section 3.5		X_d	X	X			
Whole Blood Draws (Exploratory Objectives; 3 mL)	Section 3.5		X_e	X				
Whole Blood Draws (Exploratory Objectives; 5 mL)	Section 3.5		X_f	X	X			
Whole Blood Draws (Exploratory Objectives; 20 mL)	Section 3.5		X_g	X				
Whole Blood Draws (Exploratory Objectives; 50 mL)	Section 3.5							X

Whole Blood Draws (Exploratory Objectives; 70 mL)	Section 3.5		X_a		X			

Notes:
a. Procedure must be performed prior to vaccination.
b. Two blood draws (2 x 10 ml) and two urine samples must be taken at Study Day 1, i.e. at baseline (prior to vaccination) and at 24h after vaccination.
c. Vital signs will be measured at 30 min and 24h. Additional body temperature measurement must be performed at 2, 4, 6, 8, 10, 12 and 18h after vaccination.
d. Three Serum Blood Draws (3 x 5ml) must be taken at Study Day 1, i.e. at baseline (prior to vaccination), at 6h and at 24h after vaccination.
e. Six Whole Blood Draws (6 x 3 mL) must be taken at Study Day 1, i.e. at baseline (prior to vaccination) and at 1, 2, 4, 8 and 24h after vaccination.
f. Three Whole Blood Draws (3 x 5 mL) must be taken at Study Day 1, i.e. at baseline (prior to vaccination), at 6h and at 24h after vaccination. g. Whole Blood Draw (20 mL) at Study Day 1 must be taken at 24h after vaccination.

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Table 4: Time and Events Table – Follow-up Period (until Day 366)

	Visit Type	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Phone Call**	**Phone Call**	**Clinic Visit**
	Study Day	**85**	**113**	**181**	**209**	**271**	**366**
	Visit Window (Days)	**-7 to +7**	**-7 to +7**	**-7 to +7**	**-14 to +14**	**-14 to +14**	**-14 to +14**
	Visit Number	**7**	**8**	**9**	**10**	**11**	**12**
Study Event	**References**						
Safety							
Assess SAEs	Section 7.1.4	X	X	X	X	X	X
Assess AESI	Section 7.1.4.1	X	X	X	X	X	X
Assess NOCDs, medically attended AEs, AEs leading to withdrawal	Sections 7.1.3	X	X	X	X	X	X
Assess relevant medications	Sections 5.1.2 and 6.5	X	X	X	X	X	X
Blood draws for Immunogenicity and Exploratory Objectives							

Serum Blood Draw (Secondary Objective; 10 mL)	Section 3.5			X			
Whole Blood Draw (Exploratory Objectives; 50 mL)	Section 3.5			X			
Study Completion Procedures							
Study Termination[a]	Section 5.5						X

Notes:
a. Subjects who terminate the study early are recommended to complete certain study-related procedures. See section 5.5 for further details.

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LIST OF ABBREVIATIONS

ADCC	Antibody-dependent cell mediated cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BZN	Benzonaphthyridines
CBER	Center for Biologics Evaluation and Research
cDNA	Complementary deoxyribonucleic acid
CI	Confidence interval
CRF	Case report form
CRM_{197}	Cross Reacting Material 197
CSR	Clinical Study Report
DMC	Data Monitoring Committee
EC	Ethics committee
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
ELISPOT	Enzyme-Linked ImmunoSpot
EMA	European Medicines Agency
FACS	Fluorescence-activated cell sorting
FAS	Full analysis set
FDA	Federal Drug Agency
GCP	Good clinical practice
GMC	Geometric mean concentration
GMP	Good manufacturing practice

GMT	Geometric mean titer
GMR	Geometric mean ratio
HEENT	Head, ears, eyes, nose and throat
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
hSBA	Human complement serum bactericidal assay
ICF	Informed consent form
ICH	International Committee for Harmonization
IM	Intramuscular
IRB	Institutional review board
IV	Intravenous
LLQ	Lower limit of quantification
MenC	Meningococcal type C
MPL	Monophosphoryl lipid A
NCR	No carbon required
NOCD	New Onset of Chronic Disease
PEG	Polyethylene glycol
PO	Per oral
PP	Per protocol
RNA	Ribonucleic acid (RNA
SAE	Serious Adverse Event
SMIP	Small molecule immune potentiator
TLR	Toll-like receptor
VSAE	Vaccine serious adverse event

1.0 BACKGROUND AND RATIONALE

1.1 Background

MenC-CRM$_{197}$ Conjugate Vaccine

Meningococcal disease worldwide is predominantly a disease of infants and young children. *N. meningitidis* serogroup B and C remain the most prevalent strains in North America and Europe, (Rosenstein, N. et al., 2001) and together cause more than 95% of reported cases of meningococcal disease in Europe (Connolly, M, et al., 1999). In Europe, *N. meningitidis* serogroup C (MenC) is one of the major serogroups causing invasive disease. Case fatality in Germany has ranged between 6% and 8% between 1999 and 2006, and has remained generally consistent across the different European countries, varying between 6-11%, with the case fatality rate being notably higher for serogroup C disease than for serogroup B (European Centre for Disease Prevention and Control, 2011). Since MenC vaccination was added to Germany's routine schedule for children in 2006, there has been a reported decline in MenC incidence. However, the decline was not as rapid when compared to other European countries (Hellenbrand, W. et al., 2013).

The GSK Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) comprises MenC oligosaccharides conjugated to the protein carrier, CRM$_{197}$, a nontoxic mutant of diphtheria toxin. The vaccine has been shown to be safe and immunogenic and able to prime infants, toddlers and young children for immunological memory (see Meningococcal C-CRM$_{197}$ Conjugate Vaccine Summary of Product Characteristics).

In Germany, the Standing Committee on Vaccination (STIKO) of the Robert Koch Institute recommends a single dose of MenC conjugate vaccine in children over the age of 12 months as part of the routine vaccination campaign (Robert Koch Institute Epidemiologisches Bulletin, August 2013). For specific indications, e.g. in case of postexposure prophylaxis, the recommended schedule for primary immunization of infants between 2 to 12 months of age with a MenC conjugate vaccine is two dosages given with an interval of at least 2 months.

Although the Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) represents an example of how vaccination with a well characterized, purified polysaccharide antigen can yield pivotal public health triumphs, there remains a need for further improvement of the MenC vaccine. A more potent MenC vaccine formulation might yield an increase in the magnitude of the antigen-specific immune response enabling a reduction of the antigen dosage. Furthermore, induction of a more rapid antigen-specific immune response may enable a reduction in the number of doses needed for post-exposure prophylaxis in infants.

Vaccine Adjuvants

Immunization with purified protein or polysaccharide antigens typically results in the induction of a modest antibody response with little or no T cell response when compared to vaccines comprised of whole or killed bacteria or viruses that have inherent immunepotentiating activity. The need to increase the immunogenic response of wellcharacterized and purified antigens that display suboptimal immunogenicity when used alone affirms the essential role for the use of adjuvants. Vaccine adjuvants may significantly reduce the amount of antigen needed (Del Giudice, G, et al., 2013) and may induce a more rapid immune response enabling a reduction in the number of doses in a regimen.

Besides reducing the antigen dosage or number of doses in the vaccine regimen, there is now an increased appreciation of the capacity of adjuvants to increase not just overall antibody titer but also to increase the number of functional antibodies and/or antibodies with higher affinity for vaccine antigens. Many pathogens, such as influenza viruses, HIV, human papilloma virus (HPV) and the malaria parasite, display substantial antigenic drift, subtype and/or strain variations. Therefore, the ability of adjuvants to broaden an immune response profile could be crucial to the success of vaccines against such targets. Previous studies have shown that the broadening effect of adjuvants may be mediated via expansion of B cell diversity, not merely through increased titers (Khurana, et al., 2010, 2011). Clinically, antibody response broadening by adjuvants such as AS04 or oil-inwater emulsions has been demonstrated in HPV vaccines and influenza, respectively (Bissett, SL et al., 2014; Del Giudice, G et al., 2013).

One unmet need is the development of vaccines for effective T cell responses. Several vaccines in development are aimed at eliciting T cell responses, which historically have not been induced by the most commonly used adjuvants in vaccines for human use, such as aluminium hydroxide. Therefore, an objective of many adjuvant discovery and development programs is to elicit more effective engagement of T-helper cells for optimizing the quality, breadth and durability of antibody responses, or, to induce effector CD4+ or CD8+ T cells to kill intracellular pathogens. One approach for new generation vaccines is the use of agonists for Toll-like receptors (TLRs) that activate innate immune receptors, mainly on antigen presenting cells, and facilitate the generation of T helper cell responses.

Adjuvants that are currently employed in human vaccines licensed for use in the USA and/or Europe include aluminium salts, oil-in-water emulsions (MF59, AS03 and AF03), virosomes, and AS04 (Alving, CR, et al., 2012). Among the most advanced adjuvants systems is AS04 which is used in the Cervarix® HPV vaccine and consist of the TLR4 ligand monophosphoryl lipid A (MPL) combined with aluminium salt. MPL, along with

QS21, is also part of the adjuvant system (AS01) in the RTS, S malaria vaccine which has been evaluated in a Phase 3 clinical trial (Regules, JA, et al., 2011). Another clinically advanced adjuvant is CpG oligodeoxynucleotide (ODN), a TLR9 ligand contained in the Heplisav® vaccine candidate for hepatitis B from Dynavax, that has completed a Phase 3 clinical trial (Reed, SG, et al., 2013).

Small molecule immune potentiators as a new class of vaccine adjuvants

A new class of adjuvants, small molecule immune potentiators (SMIPs), has been identified that activate immune cells by targeting TLR7 and TLR8. Imiquimod and Resiquimod (R848) are clinically advanced TLR7 and/or TLR8 SMIPs that are used as immunotherapeutics. Although Imiquimod and Resiquimod have been studied extensively as vaccine adjuvants in preclinical models (Vasilakos et al. 2013), they were never optimized for this use and, in general, compare poorly to other pre-clinical and clinical adjuvant candidates. Furthermore, when Imiquimod is applied topically (it is a licensed topical treatment for viral and malignant skin lesions) it induces strong local and systemic inflammatory reactions, and is poorly tolerated (Bauza, et al. 2009; Campanelli, et al. 2005; Meyer, et al. 2008).

Unlike traditional drugs, TLR7 SMIPs activate innate immunity and initiate a cascade of immune responses that can have systemic impact and endure after the compound has been cleared from the organism. For SMIPs as vaccine adjuvants this difference is highlighted further by the fact that 2-3 local IM injections drive antigen-specific B and T cell responses at distal sites and these can provide protection in the form of immunologic memory (Tacken, et al. 2011; Ilyinskii, et al., 2014). Therefore, limiting the systemic exposure of the SMIP adjuvants has been postulated as an approach to both increase vaccine efficacy and minimize side effects associated with systemic and generalized inflammation. GSK is currently developing a novel adjuvant, containing a SMIP from the benzonaphthryridines (BZN) series, LHD153, which targets TLR7. The objective driving the discovery of this new TLR7 ligand was to develop a vaccine adjuvant with high efficacy in increasing the vaccine specific immune response and with minimal side effects. To obtain this objective it was postulated that the ideal compound would remain localized at the site of injection to help trigger the immune reaction to vaccine antigens, yet maintain a low systemic distribution. At the same time this compound had to be soluble to make industrial scale-up and manufacturing feasible. Soluble BZN were engineered so that they could be formulated with aluminium salts with the aim of limiting their systemic exposure and keeping them localized in the muscle for short time after immunization. The strongest adsorption to aluminium hydroxide particles is obtained through ligand exchange of hydroxyl and/or phosphate groups on the surface of aluminium hydroxide or phosphate with soft anionic moieties such as phosphates, phosphonates, phosphites, sulfates and carboxylates. To drive the adsorption to

aluminium hydroxide through ligand exchange, LHD153 was functionalized with a polyethylene glycol (PEG) linker and a terminal phosphonate. Furthermore, LHD153 was stabilized with arginine salt to allow scale up for GMP manufacturing, yielding LHD153R. As predicted, unformulated LHD153R exhibited high levels of systemic exposure when injected IM in mice, rats and dogs, whereas the serum concentrations of LHD153R adsorbed to aluminium hydroxide (Aluminium Hydroxide/LHD153R) was dramatically reduced. Moreover, Aluminium Hydroxide/LHD153R remained localized to the injection site.

Preclinical studies using Aluminium Hydroxide/LHD153R to date confirm the activation of the TLR7 pathway and subsequent boost of both the humoral and cellular immune response. Moreover, Aluminium Hydroxide/LHD153R displays a unique pharmacokinetic profile as demonstrated by its minimal systemic exposure, potentially minimizing any systemic inflammatory response associated with tolerability issues. Aluminium hydroxide/LHD153R has achieved proof of concept in animal models using several vaccine antigens including MenC, MenB, rabies, HIV and respiratory syncytial virus (RSV). In vitro toxicity of LDH153R has been assessed, and in vivo nonclinical tolerability and safety of LHD153R and Aluminium Hydroxide/LHD153R have been evaluated in rats, dogs and non-human primates. LHD153R was not phototoxic, genotoxic or mutagenic (Ames and chromosomal aberration tests), and did not cause local or systemic toxicity in dogs or rats. Furthermore, Aluminium Hydroxide/LHD153R was well tolerated in rhesus monkeys.

1.2 Rationale

The aim of this study is to assess the safety of Aluminium Hydroxide/LHD153R adjuvanted MenC-CRM$_{197}$ conjugate vaccine (MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R) and to compare the antibody-mediated immune response elicited by MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R with the licensed aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®).

Furthermore, a comprehensive set of exploratory objectives has been selected to assess the systemic exposure of LHD153 after intramuscular injection and to evaluate the quality of the specific immune response against MenC-CRM$_{197}$ in detail and to evaluate biomarkers that may be predictive of safety and/or innate immune activation.

The licensed Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) has been chosen as the primary vaccine candidate to assess the safety and immunopotentiating properties of Aluminium Hydroxide/LHD153R for several reasons. Firstly, the safety and immunogenicity profiles of the Meningococcal C-CRM$_{197}$ Conjugate Vaccine have been well established through years of commercial use. Secondly, a more potent

Meningococcal C-CRM$_{197}$ Conjugate Vaccine might enable a reduction of the antigen dosage or the number of doses needed in infants between 2 and 12 months of age. Finally, Meningococcal C-CRM$_{197}$ is a well-characterized, single conjugate antigen preparation which provides an ideal setting to explore the potential of this new Aluminium Hydroxide/LHD153R adjuvant.

2.0 OBJECTIVES

2.1 Primary Objectives

Primary Safety Objective

To assess the safety of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R as compared to that of aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine.

Primary Immunogenicity Objective

To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine at Day 29, as measured by human complement serum bactericidal assay (hSBA) directed against MenC.

2.2 Secondary Objectives

Secondary Immunogenicity Objective(s)

1. To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal CCRM$_{197}$ Conjugate Vaccine at Day 8 and Day 181 after vaccination, as measured by hSBA directed against MenC. Baseline antibody titers will also be measured by hSBA.
2. To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal CCRM$_{197}$ Conjugate Vaccine, at Day 8, Day 29 and Day 181 after vaccination, as measured by an enzyme-linked immunosorbent assay (ELISA) to MenC. Baseline antibody concentrations will also be measured by ELISA.

2.3 Exploratory Objectives

1. To evaluate the systemic exposure of LHD153 at several early time-points after IM injection of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R or Meningococcal CCRM$_{197}$ Conjugate Vaccine.
2. To explore the frequency of B cells specific for MenC polysaccharide and CRM$_{197}$ protein at baseline (Day 1) and at Day 8, Day 29 and Day 181 after vaccination with MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R or the aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine. Subsequently, the B cell repertoire of the antigen specific B cells will be analyzed in a selected subset of subjects.
3. To explore the baseline T cell mediated immunity to CRM$_{197}$ and to evaluate the frequency and quality of CRM$_{197}$ specific T cells induced by MenCCRM$_{197}$/Aluminium Hydroxide/ LHD153R compared to aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine at Day 8 and Day 29.
4. To evaluate biomarkers that may be predictive for safety and/or innate immune activation.

3.0 STUDY DESIGN

3.1 Overview of Study Design

This is a Phase 1, randomized, observer blind, adjuvant dosage-escalation study. It will be performed at a single center. In total, approximately 80 healthy male and healthy nonpregnant female adults (18-45 years of age) will be enrolled in the study.

Subjects will be randomized to receive a single IM vaccination of either the licensed aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (Menjugate®) or the investigational vaccine, MenC-CRM_{197}/Aluminium Hydroxide/LHD153R.

The dosage of LHD153R will be escalated from 12.5 µg to 100 µg. For the dosageescalation of LHD153R, the subjects will be enrolled into 1 of 4 cohorts, in a stepwise manner with 20 subjects per cohort. Subjects in all cohorts will be randomized in a 1:4 ratio, to receive either aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (control) or MenC-CRM_{197}/Aluminium Hydroxide/LHD153R with increasing doses of LHD153R. Subjects assigned to MenC-CRM_{197}/Aluminium Hydroxide/LHD153R in Cohort 1 will receive 12.5 µg of LHD153R; Subjects in Cohort 2 will receive 25 µg of LHD153R; Subjects in Cohort 3 will receive 50 µg of LHD153R; Subjects in Cohort 4 will receive 100 µg of LHD153R (Table 3.1-1).

Table 3.1-1: Subjects Randomized per Cohort and Treatment Dosage Group

Cohort	Group	Subjects/ Group	MenC Dosage* (µg)	Adjuvant Dosages		Total Volume/Dose	Total Subjects/Cohort
				Aluminium Hydroxide (mg)	LHD153R (µg)		
1	A	4	10	1	0	0.5 mL	20
	B	16	10	1	12.5	0.5 mL	
2	A	4	10	1	0	0.5 mL	20
	C	16	10	1	25	0.5 mL	
3	A	4	10	1	0	0.5 mL	20
	D	16	10	1	50	0.5 mL	
4	A	4	10	1	0	0.5 mL	20
	E	16	10	1	100	0.5 mL	

*Conjugated to 12.5-25 µg CRM_{197}

All cohorts will have a staggered entry. For each cohort, the first 5 subjects (i.e. the first 1:4 randomization block) to receive either aluminium hydroxide adjuvanted

Meningococcal C-CRM$_{197}$ Conjugate Vaccine (n=1) or MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R (n=4) will be vaccinated at rate of 1 subject each day.

After entry of the first 5 subjects in each cohort, the enrollment will be paused. The remaining 15 subjects for each cohort will be enrolled only after DMC review of the safety results obtained through Day 14 has been finalized (Table 3.1-2). In addition, enrollment of the first 5 subjects of the next cohort will only proceed after the Day 14 safety results of the first 5 subjects of the previous cohort have been reviewed by the DMC. Furthermore, all available Day 14 and Day 29 safety results will be included in DMC review between the different enrollment stages.

Table 3.1-2: Overview of staggered entry of subjects based on DMC reviews

Stage	Dosage Cohort	MenC-CRM$_{197}$/ Aluminium Hydroxide (n)	MenC-CRM$_{197}$/ Aluminium Hydroxide /LHD153R (n)
1	1	1	4
Enrollment pause until DMC review of Stage 1 Day 14 Safety Results			
2	1	3	12
	2	1	4
Enrollment pause until DMC review of Stage 1 Day 29 and Stage 2 Day 14 Safety Results			
3	2	3	12
	3	1	4
Enrollment pause until DMC review of Stage 2 Day 29 and Stage 3 Day 14 Safety Results			
4	3	3	12
	4	1	4
Enrollment pause until DMC review of Stage 3 Day 29 and Stage 4 Day 14 Safety Results			
5	4	3	12

Post-vaccination procedures include collection of urine specimens at Day 1, Day 8 and Day 29 for safety assessment and blood specimens at Day 1, Day 8, Day 29 and Day 181 for safety assessment and evaluation of the primary and secondary immunogenicity endpoints. Furthermore, additional blood specimens will be collected for assessment of exploratory endpoints at Day 1, Day 4, Day 8, Day 29 and Day 181 from those subjects that signed an additional informed consent concerning blood collection for exploratory assessment.

3.2 Study Period

Each subject should expect to participate in the study for approximately 12 months, from the time of enrolment through the last study visit.

3.3 Blinding Procedures

This study is designed as an observer-blind study. For each dosage cohort, subjects, investigators, laboratories and the sponsor will be blinded to vaccine assignments.

To maintain the blindness within each cohort, designated nurse(s) or physician(s) will be responsible for administering the study vaccines to the subjects, and will be instructed not to reveal the identity of the study vaccines neither to the subject nor to the investigative site personnel (investigator, study nurse, monitor) involved in the conduct or monitoring of the trial. This (these) designated individual(s) will have no contact with the subjects after the administration of the study vaccine. Furthermore, unblinded monitors are assigned to reconcile actual vaccine treatment.

Study unblinding, at the group level, is planned for an Interim Analysis of the safety and immunogenicity data obtained up to Day 29 after all cohorts are enrolled and for full unblinding at the End of Study.

Except in the case of medical necessity, a subject's treatment should not be unblinded without the approval of the Sponsor. In such instance of medical emergency, every effort should be made to contact the Sponsor prior to unblinding. If unblinding should occur (by either accidental unblinding or emergency unblinding for a serious adverse event) prior to completion of the study, the investigator must promptly contact the Sponsor and document the circumstances on the appropriate forms.

Emergency unblinding

Emergency unblinding should only be undertaken when it is essential for effective treatment of the subject. The investigator will receive a blinded code break envelope for each subject, with the details of drug treatment included. Emergency code break envelopes must be stored in a secure place but be accessible in case of emergency. In an emergency, the envelope can be opened to determine the treatment. The envelope is not to be opened for any reason other than an emergency. When the investigator opens the envelope he/she must note the date, time, and reason for opening it and retain this information with the case report form documentation. The unblinded treatment code should not be recorded in the case report form.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the code break envelope in case of emergency. The investigator must provide the subject with an emergency card to contact the clinical unit in cases of emergency and will inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable. Subjects may continue the study after unblinding for safety follow-up.

For emergency unblinding, the corresponding Parexel standard operating procedure should be followed:

- Annotate, sign and date the code break envelope.
- Immediately inform Sponsor.
- Complete the Randomization Code Break Form.
- File the Randomization Code Break Form and the annotated envelope with the participant's source documents.
- Provide the Sponsor as soon as feasible, with a copy of the completed Randomization Code Break Form.

3.4 Data Collection

3.4.1 Data Collected from Subjects

The following data will be collected from each subject over the duration of their study participation:

- Demographic Information
- Adverse Events
- Medical History
- Concomitant Medications
- Vital signs

All data collected must only be identified using the Subject ID, as described in section 5.2.3.

3.4.2 Tools Used for Data Collection

Data will be recorded in the Subject Diary and collected on Case Report Forms (CRFs).

Subject Diary

Subject Diaries will be the only source document allowed for solicited local and systemic adverse events (including body temperature measurements), starting after the initial 24 hours post-vaccination observation period at the clinic. The following additional rules apply to documentation of safety information collected in the Subject Diary:

1. No corrections or additions to the Subject Diary will be allowed after it is delivered to the site.
2. Any blank or illegible fields on the Subject Diary must be described as missing in the CRF.
3. Any corrections to the Subject Diary must be performed by the person completing the Subject Diary and should include a single strike through line through the incorrect value or text with a brief explanation for each change, the initials of that person, and date of correction.

Case Report Forms

This study utilizes CRFs to collect study-related data from each subject. A qualified site staff member(s) is required to enter subject data in the CRFs based on the medical information available in each subject's record. The following additional rules apply to documentation of Subject Diary information collected in the CRFs:

1. The site must enter all readable entries in the Subject Diary into the CRF, including those values that may be biologically implausible (e.g. body temperature: 400°C).
2. Any illegible or implausible data should be reviewed with the subject. If an underlying solicited or unsolicited adverse event is described on review with the subject, this should be described in the source document and reported as an unsolicited adverse event in the appropriate CRF (e.g., if the subject above confirms body temperature of 40°C on the day in which body temperature: 400°C was written into his/her Subject Diary, this fever of 40°C should be recorded in the appropriate CRF).
3. Any newly described safety information (including a solicited adverse event) must not be written into the Subject Diary and must be described in the study file as a verbally reported adverse event. Any adverse event reported in this fashion must be described as an unsolicited adverse event and therefore, entered in the appropriate CRF.

Data should be entered into the CRF in a timely fashion following each subject's clinic visit, study procedure, or phone call. Each subject's CRF casebook will be compared with the subject's source records by a GSK-approved study monitor (or designee) over the duration of the study in order to ensure data collection accuracy.

3.5 Collection of Clinical Specimens

The following clinical specimens are required to be collected from each subject in this study:

- Blood
- Urine

Processing of each specimen should be completed by a qualified site member. Testing of clinical specimens will be performed by a GSK or designated laboratory.

Blood Specimens

Before Vaccination

- At the Pre-vaccination Screening Visit (between Day -28 to -3) one sample of approximately 10 ml blood will be drawn from all subjects.
- At Visit 1 (Day 1) - prior to vaccination – two samples of approximately 10 ml blood will be drawn from all subjects.
- At Visit 1 (Day 1) - prior to vaccination - the following blood samples will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays:
  - One sample of approximately 3 ml
  - Two samples of approximately 5 ml
  - One sample of approximately 70 ml

After Vaccination

- At Visit 1 (Day 1) - 1 hour after vaccination - one sample of approximately 3 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 2 hours after vaccination - one sample of approximately 3 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 4 hours after vaccination - one sample of approximately 3 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 6 hours after vaccination – two samples of approximately 5 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.

- At Visit 1 (Day 1) - 8 hours after vaccination - one sample of approximately 3 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 24 hours after vaccination - one sample of approximately 10 ml blood will be drawn from all subjects.
- At Visit 1 (Day 1) - 24 hours after vaccination - the following blood samples will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays:
  - One sample of approximately 3 ml
  - Two samples of approximately 5 ml
  - One sample of approximately 20 ml
- At Visit 2 (Day 4) the following blood samples will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays:
  - One sample of approximately 3 ml
  - Two samples of approximately 5 ml
  - One sample of approximately 20 ml
- At Visit 3 (Day 8) two samples of approximately 10 ml blood will be drawn from all subjects.
- At Visit 3 (Day 8) the following blood samples will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays
  - Two samples of approximately 5 ml
  - One sample of approximately 70 ml
- At Visit 6 (Day 29) two samples of approximately 10 ml blood will be drawn from all subjects.
- At Visit 6 (Day 29) one sample of approximately 50 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 9 (Day 181) one sample of approximately 10 ml blood will be drawn from all subjects.

- At Visit 9 (Day 181) one sample of approximately 50 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.

The blood will be used for screening and safety laboratory assessments, immunological serology assays, pharmacokinetic analysis, cell mediated immunity assays and gene expression and protein production assays. See section 5.1.2, section 5.2.1 and section 7.0 for additional details.

Processing of each blood specimen should be completed in accordance with the study specific Clinical Specimen Laboratory Manual.

The total amount of blood collected over the study period for all subjects will be approximately 90 ml.

For subjects that signed an additional informed consent for blood collection for exploratory assays the total amount of blood collected over the study period will be approximately 441 ml.

Urine Specimens

Urine will be collected at the Pre-vaccination Screening Visit (between Day -28- to -3), at Visit 1 (Day 1; before vaccination and 24 hours after vaccination), at Visit 3 (Day 8) and at Visit 6 (Day 29). Results will be recorded in the source document and CRF.

Urine will be collected from all subjects for safety laboratory assessments and drugs-ofabuse testing. Furthermore, urine will be collected for pregnancy testing in all females.

3.6 Stopping/Pausing Guidelines

Stopping/pausing guidelines are predefined criteria that halt the conduct of a study (either a vaccine group or the entire study). These guidelines are used to ensure the safety of study subjects.

The following criteria, based on FDA guidance and with grading scales adapted from the CBER Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive vaccine Clinical Trials", will be used for this study:

1. The study will be halted (no new enrollments and no further investigational product administered) and a full safety review by the DMC and the IRB/EC will be performed if one of the following occurs.

a. One subject experiences a serious adverse event (SAE) assessed as possibly or probably related to investigational product or,

b. There is a subject death assessed as possibly or probably related to the investigational product.

2. The safety data will also be provided to the health authorities and potential restart of the study will require authorization from IRB/EC and health authorities.If one or more subjects experience a Grade 4 AE (see Appendix C, D, E and F for grading scales), vital sign or clinically significant laboratory abnormality that cannot be clearly attributed to another cause, vaccination will be suspended and a full safety review by the DMC and the IRB/EC will be performed. Potential continuation of the study will require authorization from IRB/EC.

3. If six or more subjects experience a Grade 3 AE (see Appendix A, B, C, D, E and F for grading scales), vital sign or clinically significant laboratory abnormality, dosage escalation will be suspended for that vaccine and a full safety review by the DMC and the IRB/EC will be performed. Potential continuation of the study will require authorization from IRB/EC.

The sponsor or the investigator (following consultation with the sponsor) has the right to discontinue the study at any time. If the clinical study is prematurely terminated, the investigator must promptly inform the study subjects and must assure appropriate therapy and follow-up for the subjects. All procedures and requirements pertaining to the archiving of the documents must be followed. All other study materials (such as study vaccines) must be returned to the sponsor or destroyed after sponsor approval.

3.7 Data Monitoring Committee

An independent DMC will be formed to review safety data during scheduled periodic reviews. The DMC may also perform reviews on an ad hoc basis as needed. DMC membership will consist of at least 3 individuals who are external to the site and sponsor, and will include 1 statistician who is independent from the study team. The names of the independent DMC members are mentioned in the DMC charter.

Subjects will be enrolled in a stepwise manner in each of the four vaccine dosage cohorts (Cohort 1: 12.5 µg LHD153R, Cohort 2: 25 µg of LHD153R, Cohort 3: 50 µg of LHD153R and Cohort 4: 100 µg of LHD153R). The DMC will review all safety data, as described in the DMC charter and in the Statistical Analysis Plan, after the first 5 subjects in each cohort have completed Visit 4 and their data are available for analysis, and before enrollment of the remaining subjects in the respective cohort and before enrollment of the first 5 subjects in the subsequent cohort. In addition, in between the different enrollment

stages, the DMC will review all available safety data of subjects that have completed Visit 4 and all available safety data of subjects that have completed Visit 6.

The specific roles and responsibilities of the DMC members and other personnel involved will be documented in the DMC charter. The DMC charter will be finalized before the start of the study and will outline in detail all pausing and stopping rules according to the Clinical Study Protocol.

3.8 Premature Withdrawal from Study

Subjects may withdraw at any time, or be dropped from the study at the discretion of the investigator should any untoward effects occur and/or for safety reasons. In addition, a subject may be withdrawn by the investigator or the Sponsor if he/she violates the study plan or for administrative reasons. The investigator or study coordinator must notify the Sponsor immediately when a subject has been withdrawn due to an adverse event.

The circumstances above are referred to as premature withdrawal from the study, and the reason for premature withdrawal should be clearly documented and detailed in the source documentation. The investigator should make every attempt to evaluate the subject's safety, including resolution of ongoing AEs, at the time of premature withdrawal. If a subject wants to withdraw from the study prior to the last planned study visit, the subject will be asked to be followed for safety for the duration of the study. When a subject withdraws, or is withdrawn, from the study, the procedures described in section 5.5.1 should be completed if possible.

The reasons for premature withdrawal from the study include: Adverse event, death, withdrawal of consent, lost to follow-up, administrative reason, and protocol deviation. These reasons are described in greater detail below.

Adverse Event

For any subject withdrawn from study participation prior to the planned Study Termination Visit, it is important to determine if an AE was associated with the reason for discontinuing the study. This AE must be identified on the appropriate CRF page by indicating "Withdrawn from study due to AE". Any ongoing AEs at the time of study withdrawal must be followed until resolution or stabilization.

Death

For any subject withdrawn from study participation due to death, this should be noted on the appropriate CRF page and the associated SAE that led to the death must be reported.

Withdrawal of consent

The subject can withdraw consent for participation in the study at any time without penalty or loss of benefit to which the subject is otherwise entitled. Reason for early termination should be deemed as "withdrawal of consent" if the subject withdraws from participation due to a non-medical reason (i.e., reason other than AE). If the subject intends to withdraw consent from the study, the investigator should clarify if the subject will withdraw completely from the study or if the subject will continue study participation for safety, or a subset of other study procedures. If the subject requests complete withdrawal from the study, no further study interventions will be performed with the subject.

Lost to Follow-Up

For subjects who fail to show up for study visits (clinic or telephone contacts), study staff is encouraged to make at least three documented attempts to contact the subject by telephone and at least one documented written attempt to contact the subject to encourage the completion of study termination procedures. These efforts to contact the subject must be recorded in the source document. The termination date for the subject to be captured on the appropriate CRF page is the date of the last contact (clinic visit or telephone) with the subject.

Administrative Reason

Examples for subjects withdrawn from the study due to administrative reason can include: Sponsor decision to terminate the study, subject meeting a pre-specified withdrawal criterion, subject discontinuation for insurance issues, moving, no time, etc. This reason should be noted in the appropriate CRF page and any ongoing AEs at the time of study withdrawal must be followed until resolution/stabilization.

If the clinical study is prematurely terminated by the Sponsor, the investigator is to promptly inform the study subjects and local EC/IRB and should assure appropriate therapy and follow up for the subjects. All procedures and requirements pertaining to the archiving of study documents should be followed. All other study materials (study medication/vaccines, etc.) must be returned to the Sponsor.

For subjects who are withdrawn from the study due to receipt of an excluded medication/vaccination or due to significant protocol non-compliance, this reason should be noted in the appropriate CRF page.

Protocol Deviation

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. In general, subjects associated with protocol deviations may remain in the study unless continuation in the study jeopardizes the subject's health, safety, or rights.

Investigators will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact GSK or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a change to the protocol would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by GSK and approved by the IRB/EC and health authorities it cannot be implemented.

Any subject who becomes pregnant during the study should be encouraged to continue participating in the study for safety follow-up. The site must complete a Pregnancy Report CRF (initial report) as soon as possible after learning of pregnancy occurrence (see section 7.1.6 for further details). If the subject withdraws from the study for any of the above categories except death, the site will obtain permission from the subject to continue to remain in contact with her until the outcome of the pregnancy is known, even if the outcome is not known until after the subject reaches the end of the routine study period.

3.9 End of Study

Most clinical trials intended to support the efficacy/immunogenicity and safety of an Investigational Product proceed to full completion of planned sample size accrual.

A subject is considered to have completed this study when he/she has: (1) received the intended dose of study vaccine and (2) completed 365 days (Visit 12) of safety follow-up after receiving the study vaccine.

Evaluation of the primary and secondary immunogenicity objectives requires the testing of biological samples from all study subjects, which can only be completed after all samples are collected. The last samples for the analysis of the primary and/or secondary objectives will be taken at Visit 9 (Day 181). For the purpose of this protocol, End of Study is defined as the completion of the testing of such biological samples, to be achieved no later than 8 months after collection of the last biological sample at Visit 9.

4.0 SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

In order to participate in this study, all subjects must meet all of the inclusion criteria described.

1. Male or female individuals of 18 through 45 years of age on the day of informed consent.
2. Healthy volunteers with good physical and mental health status, determined on the basis of the medical history, a physical examination and the results of the screening tests as judged by the investigator.
3. Individuals who have voluntarily given written informed consent after the nature of the study has been explained according to local regulatory requirements, prior to study entry.
4. Individuals who can comply with study procedures including follow-up[1].
5. Individuals that are able to understand, read and write German language.
6. Females of childbearing potential who are using an effective birth control method[2] which they intend to use for at least 30 days after the study vaccination.

4.2 Exclusion Criteria

Each subject must not have or must not be:

1. Progressive, unstable or uncontrolled clinical conditions.
2. Hypersensitivity, including allergy, to any component of vaccines, medicinal products or medical equipment whose use is foreseen in this study.

[1] A subject is considered to be compliant if the Investigator judges that the subject will complete the Subject Diary, return for all the follow-up visits and be available for telephone calls as scheduled in the study.

[2] The following birth control methods are considered effective:

- Hormonal contraceptive (such as oral, injection, transdermal patch, implant) if used for at least 30 days prior to informed consent
- Diaphragm with spermicide, tubal occlusion device
- Intrauterine device (IUD)
- Tubal ligation

- Male partner using condom with spermicide
- Male partner having been vasectomized at least six months prior to informed consent

3. Clinical conditions representing a contraindication to intramuscular vaccination and blood draws.
4. Abnormal function of the immune system resulting from:
   a. Clinical conditions.
   b. Systemic administration of corticosteroids (PO/IV/IM) for more than 14 consecutive days within 90 days prior to informed consent.
   c. Administration of antineoplastic and prescription immunomodulating agents or radiotherapy within 90 days prior to informed consent.
5. Received immunoglobulins or any blood products within 180 days prior to informed consent.
6. Received an investigational or non-registered medicinal product within 30 days prior to informed consent or intend to participate in another clinical study at any time during the conduct of this study.
7. Vulnerable subjects (e.g. persons kept in detention), study personnel or an immediate family or household member of study personnel, subjects with legal incapacity or limited legal capacity
8. Any relevant deviation from the laboratory parameters at screening as judged by the investigator.
9. Previously received any vaccine that included a MenC antigen.
10. Previously suspected or confirmed disease caused by *N. meningitides.*
11. Had household contact with and/or intimate exposure to an individual with culture proven MenC.
12. A positive serum or urine pregnancy test prior to the study vaccine administration or are currently lactating.
13. A positive drugs-of-abuse test prior to the study vaccine administration
14. Received any other vaccines within 30 days prior to enrolment in this study or who are planning to receive any vaccine within 30 days from the administration of study vaccines.

15. Any other condition that, in the opinion of the investigator, might interfere with the results of the study or pose additional risk to the subject due to participation in the study.

4.3 Criteria for Delay of Vaccination or Blood Draw

There may be instances when individuals meet all eligibility criteria for vaccination or blood draw yet have a transient clinical circumstance which may warrant delay of vaccination or blood draw. Under such circumstances, a subject may be considered eligible for study enrolment after the appropriate window for delay has passed and inclusion/exclusion criteria have been rechecked, and if the subject is confirmed to be eligible.

Reasons for delay of vaccination include:

- Body temperature elevation ≥38.0°C (measured orally) within 3 days prior to intended study vaccination.
- Use of antipyretics and/or analgesic medications within 24 hours prior to vaccination.

Reasons for delay of blood draw include:

- Subject has received a dose of systemic antibiotics less than 6 days before blood collection for the hSBA directed against MenC.

5.0 STUDY PROCEDURES

The sections that follow provide an overview of the procedures that are to be followed in enrolling, evaluating, and following subjects who participate in this clinical study. Visits can be either clinic visits or safety follow-up telephone calls, as specified in the Table below and in the Time and Events Tables 3 and 4 of the Study Synopsis.

Table 5.0-1: Study procedures

Visit Category	Procedures
Pre-vaccination Clinic Visit	Section 5.1 describes procedures to be followed prior to subject enrollment, including: informed consent and screening procedures.
Vaccination Clinic Visit	Section 5.2 describes procedures to be followed during the vaccination clinic visit, including: prevaccination procedures, enrolment, randomization, vaccination and post-vaccination procedures.
Post-vaccination Visits	Section 5.3 describes follow-up clinic visits and safety follow-up calls.
Unscheduled Visits	Section 5.4 describes possible procedures to be followed at unscheduled clinic visit.
Study Termination Visit	Section 5.5 describes procedures to be followed at the last study visit for a subject (may include early termination visit).

5.1 Pre-vaccination Clinic Visit(s)

The Pre-vaccination Clinic Visit must be performed in the period between Day -28 and Day -3.

This section describes the procedures that must be performed for each potential subject prior to enrollment, including obtaining informed consent and screening.

5.1.1 Informed Consent

"Informed consent" is the voluntary agreement of an individual or his/her legal guardian(s) to participate in research. Consent must be given with free will of choice, and without undue inducement. The individual must have sufficient knowledge and understanding of the nature of the proposed research, the anticipated risks and potential benefits, and the requirements of the research to be able to make an informed decision.

Informed consent following local IRB/EC guidance **must** be obtained before conducting any study-specific procedure (i.e., all of the procedures described in the protocol). Prior to any additional blood sample collection for exploratory objectives, a secondary informed consent **must** be signed by subjects. The process of obtaining informed consent should be documented in the subject source document in addition to maintaining a copy of the signed and dated informed consent.

5.1.2 Screening

After an individual has consented to participate in the study and informed consent is signed, that individual will be given a unique Screening Number. The subject's unique Screening Number will be documented in the Screening and Enrolment log. The eligibility of the subject will be determined based on the inclusion and exclusion criteria listed in section 4.0 and evaluated during this screening procedure.

Screening procedures at the Pre-vaccination Clinical Visit (between Day -28 and Day -3) will include the following:

- Review of demographic data, including age, gender, race, body weight and height.
- Review of medical history, including but not limited to any medical history, ongoing illnesses or injuries that may be relevant to subject eligibility for study participation. Relevant medical history can also include any medical history that contributes to the understanding of an adverse event that occurs during study participation, if it represents an exacerbation of an underlying disease/pre-existing problem.
- Perform physical examination, including but not limited to:
  - Assessment of general appearance
  - Collection of vital signs, including body temperature, blood pressure, heart rate and respiratory rate
  - Examination of head, ears, eyes, nose and throat (HEENT)
  - Examination of skin
  - Auscultation of heart and lungs
- Collection and review of prior and concomitant medications or vaccinations taken prior to start of study (refer to section 6.5 for further details).
- Collection of any unsolicited AEs occurring prior to administration of the study vaccine.

- Blood draw (approximately 10 ml) for Safety Laboratory assessments, measurement of Hepatitis B surface antigen, anti-Hepatitis C virus antibodies, anti-HIV 1 and 2 antibodies and serum pregnancy test (all women).
- Urine sample for Safety Laboratory assessments and drugs-of-abuse testing.

NOTE: A general physical examination is to be performed by a qualified health care practitioner. "Qualified health care practitioner" refers to any licensed health care professional who is permitted by institutional policy to perform physical examinations and who is identified within the Study Staff Signature Log.

Data collected during the Pre-vaccination Screening Clinic Visit must be written in the source document (see section 9.1) and will be captured in the screening CRF Forms. In the event that the individual is determined ineligible for study participation, he/she is considered a screen failure. The reason for screen failure must be documented in the Screening and Enrolment log.

5.2 Vaccination Clinic Visit(s)

This section describes the procedures to be performed at the Vaccination Clinic Visit (Visit 1, Day 1), including: pre-vaccination procedures, enrolment, randomization, prevaccination blood draw, vaccination and post-vaccination procedures.

5.2.1 Pre-vaccination Procedures

During pre-vaccination procedures at Visit 1 (Day 1), the eligibility of the subject will be confirmed based on the inclusion and exclusion criteria listed in section 4.0.

Pre-vaccination procedures at Visit 1 (Day 1) will include the following:

- Review of systems by means of a structured interview that queries the subject as to any complaints the subject has experienced across each organ system.
- Perform physical examination, including but not limited to:
  - Assessment of general appearance
  - Assessment of body weight and collection of vital signs, including body temperature, blood pressure, heart rate, and respiratory rate
  - Examination of head, ears, eyes, nose and throat (HEENT)
  - Examination of skin
  - Auscultation of heart and lungs

- Collection and review of prior and concomitant medications or vaccinations taken, or recalled, since the last visit (refer to section 6.5 for further details).
- Collection of any unsolicited AEs occurring prior to administration of the study vaccine.
- One blood sample (approximately 10 ml) will be drawn from all subjects for serology testing.
- One blood sample (approximately 10 ml) will be drawn from all subjects for baseline Safety Laboratory assessments.
- One urine sample for baseline Safety Laboratory assessments, pregnancy testing (all women) and drugs-of-abuse testing.
- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and volume of blood draws are provided in section 3.5.

NOTE: A general physical examination is to be performed by a qualified health care practitioner. "Qualified health care practitioner" refers to any licensed health care professional who is permitted by institutional policy to perform physical examinations and who is identified within the Study Staff Signature Log.

Data collected during pre-vaccination procedures at Visit 1 must be written in the source document (see section 9.1). In the event that the individual is determined ineligible for study participation, he/she is considered a screen failure. The reason for screen failure must be documented in the Screening and Enrolment log. If the individual is determined to be eligible for the study, he/she can be enrolled into the study.

5.2.2 Enrolment

After an individual is determined to be eligible for study participation, the investigator will enroll the subject into an Electronic Data Capture (EDC) system where the randomization to the treatment group will occur. The Screening Number ceases to be used and remains in the Screening and Enrolment Log only.

If for any reason, after signing the informed consent form (ICF), the subject who is eligible and enrolled fails to be randomized, this is called a randomization failure. In this case the early termination study procedures must be applied. The reason for all randomization failures should be recorded in the Screening and Enrolment Log and in the source document as specified in the Source Data Agreement. The information on subjects

who are randomization failures should be kept distinct from subjects who are screen failures, as described in section 5.1.2 and section 5.2.1.

5.2.3 Randomization

Enrolled subjects will be randomized and automatically assigned a unique Subject ID. The Subject ID will be the subject's unique identification number for all CRFs and associated study documentation that will be used for the duration of the study.

If for any reason, after signing the informed consent form (ICF), the eligible subject is enrolled and randomized but fails to undergo treatment, this is an Early Termination and the reason should be recorded in source document as specified in the Source Data Agreement/Source Data Verification Form. The information on these Early Termination subjects should be kept distinct in the source documentation from randomization failures, which are described in section 5.2.2.

5.2.4 Vaccination

After completing the pre-vaccination procedures at Visit 1 (Day 1), administer the vaccine to the subject according to the procedures described in section 6.3. Observe the blinding procedures described in section 3.3.

5.2.5 Post-vaccination Procedures

The following post-vaccination procedures will be performed at Visit 1 (Day 1):

- After vaccination, the subject will be observed for at least 30 minutes for any immediate solicited and unsolicited AEs, body temperature measurement and vital signs at 30 min after vaccination. All safety and body temperature data collected during this time are to be recorded in the subject's source document.
- After vaccination, the subject will be observed for at least 24 hours at the clinic including observation for solicited and unsolicited AEs, body temperature measurements. Body temperature measurements must be performed at 2, 4, 6, 8, 10, 12, 18 and 24 hours after vaccination and additional vital signs at 24h after vaccination. All safety and body temperature data collected during this time are to be recorded in the subject's source.
- One blood sample (approximately 10 ml) will be drawn from all subjects at 24 hours after vaccination for Safety Laboratory assessments.
- One urine sample will be collected from all subjects at 24 hours after vaccination for Safety Laboratory assessments.

- From those subjects that signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn in the first 24 hours after vaccination. Details regarding the number and volume of post-vaccination blood draws are provided in section 3.5.

After the initial 24 hours inpatient observation period, a Subject Diary will be used in this study to document solicited and unsolicited AEs until Day 14. The Subject Diary is the only source for collection of solicited AEs after the initial 24 hours inpatient observation period. Therefore, it is critical that the subject completes the Subject Diary correctly.

The following training regarding completion of the Subject Diary must be provided:

- The subject should be trained on how and when to complete each field of the Subject Diary.
- The subject should be trained on how to self-measure local solicited adverse events and body temperature. The measurement of solicited local adverse events is to be performed using the ruler provided by the site.
- The subject should be instructed how to perform body temperature measurement using the thermometer provided by the site. If the subject feels unusually hot or cold during the day, the subject should check their body temperature. If the subject has fever, the highest body temperature observed that day should be recorded in the Subject Diary.

Subject Diary training should be directed at the individual(s) who will perform the measurements of adverse events and who will enter the information into the Subject Diary. This individual may not be the subject, but if a person other than the subject enters information into the Subject Diary, this person's identity must be documented in the Subject Diary. Any individual that writes in the Subject Diary must receive training on completion of the Diary Card at the time of the visit. This training must be documented in the subject's source record.

The site should schedule the next study activity (clinic visit) with the subject.

The subject will receive a written reminder of the next planned study activity. The subject will be reminded to complete the Subject Diary and to contact the site if there are any questions, and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

5.3 Post-vaccination Visit(s)

5.3.1 Subject Diary Reminder, Safety Follow-up and/or Post-vaccination Blood Draw Clinic Visits

Subject Diary reminder, Safety follow-up and/or post-vaccination blood draw clinic visits will be performed on Day 4 (Visit 2), Day 8 (Visit 3), Day 15 (Visit 4), Day 29 (Visit 6), Day 85 (Visit 7), Day 113 (Visit 8) and Day 181 (Visit 9)

At Day 4 (Visit 2) the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. All unsolicited AEs, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. Any concomitant medications or vaccinations associated with those events must also be recorded on the source documents.
- All subjects will be reminded to complete the Subject Diary and to contact the site if there are any questions, and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit. No changes to the Subject Diary should be done at the clinic visit.
- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and volume of blood draws are provided in section 3.5.
- The site should schedule the next study activity (clinic visit) with the subject and the subject will receive a written reminder of the next planned study activity.

At Day 8 (Visit 3) the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. All unsolicited AEs, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. Any concomitant medications or vaccinations associated with those events must also be recorded on the source documents.

- The subject will be reminded to complete the Subject Diary and to contact the site if there are any questions, and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to hospitalization or an emergency room visit. No changes to the Subject Diary should be done at the clinic visit.
- Blood draw (approximately 10 ml) from all subjects for Safety Laboratory assessments.
- Urine sample from all subjects for Safety Laboratory assessments.
- Blood draw (approximately 10 ml) from all subjects for serology testing.

- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and
- volume of blood draws are provided in section 3.5.

  The site should schedule the next study activity (clinic visit) with the subject and the subject will receive a written reminder of the next planned study activity.

At Day 15 (Visit 4) the following procedures will be performed:

- The Subject Diary will be collected and reviewed. No changes to the Subject Diary should be done at the clinic visit. For details on the Subject Diary see sections 3.4.2, and 5.2.5. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. All unsolicited AEs until Day 14, solicited local and systemic AEs persisting at Day 14, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. All concomitant medications or vaccinations associated with those events must also be recorded on the source documents.
- The site should schedule the next study activity (safety phone call) with the subject.
- The subject will receive a written reminder of the next planned study activity. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

At Day 29 (Visit 6) the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. Any solicited local and systemic AEs continuing beyond Day 14, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. All concomitant medications or vaccinations associated with those events must also be recorded on the source documents.

- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and

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- Blood draw (approximately 10 ml) from all subjects for Safety Laboratory assessments.
- Urine sample from all subjects for Safety Laboratory assessments.
- Blood draw (approximately 10 ml) from all subjects for serology testing.

volume of post-vaccination blood draws are provided in section 3.5.

The site should schedule the next study activity (clinic visit) with the subject.

- The subject will receive a written reminder of the next planned study activity. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

At Day 85 and Day 113 (Visit 7 and Visit 8), the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. Any solicited local and systemic AEs continuing beyond Day 14, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. All concomitant medications or vaccinations associated with those events must also be recorded on the source documents.
- The site should schedule the next study activity (clinic visit) with the subject.
- The subject will receive a written reminder of the next planned study activity. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

At Day 181 (Visit 9), the following procedures will be performed:

- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and

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- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. Any solicited local and systemic AEs continuing beyond Day 14, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. All concomitant medications or vaccinations associated with those events must also be recorded on the source documents.
- Blood draw (approximately 10 ml) from all subjects for serology testing.

  volume of post-vaccination blood draws are provided in section 3.5.

  The site should schedule the next study activity (safety phone call) with the subject.
- The subject will receive a written reminder of the next planned study activity. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

5.3.2 Safety Follow-up Calls

Safety follow-up calls will be performed on Day 22 (Visit 5), Day 209 (Visit 10) and Day 271 (Visit 11) and include the following procedures:

- Safety follow-up calls are calls made to the subject by a healthcare professional designated on the site log. These calls will follow a script which will facilitate the collection of relevant safety information. The subject will be interviewed according to the script, and information relating to solicited local and systemic AEs persisting beyond Day 14 and unsolicited adverse events including SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal, and/or NOCD and concomitant medications or vaccinations associated with those events. All safety information described by the subject must be written down in a designated location within the source document and not written on the script used for the telephone call.

- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and

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- The site should schedule the next study activity (clinic visit or study termination visit) with the subject.
- The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

5.4 Unscheduled Visits

An unscheduled visit describes a non-routine study visit triggered by a specific event. These could include anticipated or unanticipated adverse events or interventions.

The following procedures should be carried out for all unscheduled visits:

1. Evaluate the subject's vital signs body temperature, heart rate, and blood pressure and perform a symptom-directed physical examination.
2. Record any observed AEs in the source documents.

3. Record any concomitant medications or vaccinations associated with AEs in the source documents.

5.5 Study Termination Visit

The study termination visit is scheduled on Day 366 (Visit 12). The termination visit is a clinic visit. For visit procedures to be performed for a subject whose planned study participation ends prematurely, please see section 5.5.1.

At the Study Termination clinic visit the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit.
- The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present.
- Medically attended AEs, SAEs, NOCDs, or AESIs will be recorded on source documents.
- All medications taken or vaccines received will also be recorded on the source documents.
- The site will review with the subject the plan of when information relating to the subject's participation in the study may be available (e.g., study results, treatment assignments). It will also be discussed how information relating to the subject's participation in the study will be shared with the subject's healthcare provider, if the subject chooses to share this information.
- The site will complete the termination CRF page and this will mark the completion of the subject's participation in the study.

5.5.1 Early Termination Visit

The date of termination is the date of the last contact in which the subject's health status was assessed or, in cases where the subject does not agree to any further safety follow-up, it is the date consent is withdrawn. This date should be recorded on the appropriate CRF page.

When a subject is withdrawn from treatment or withdraws from the study, the investigator will notify the Sponsor and, when possible, will perform the procedures listed below.

The reason(s) for the early termination must be included in the subject's source documentation. If the Early Termination Visit is a telephone call, collect as much information as possible. Early Termination Visits include subjects who were randomized but not treated.

At the clinic visit or during the telephone call, the following procedures should be performed, when possible:

- Collection and review of Subject Diary (if not already collected).
- Interview of subject to collect unsolicited adverse events, medically attended AEs, AEs leading to withdrawal, SAEs, AESIs, and NOCD.
- Interview of subject to collect concomitant medications and/or vaccinations.
- Symptom-directed physical assessment, at least including measurement of vital signs (body temperature, respiratory rate, blood pressure, heart rate) and a check of general appearance (in case of clinic early termination visit).
- Draw a blood sample (approximately 10 ml) and a urine sample for Safety Laboratory assessment (in case of clinic early termination visit).
- The site will review with the subject the plan of when information relating to the subject's participation in the study may be available (e.g., study results, treatment assignments). It will also be discussed how information relating to the subject's participation in the study will be shared with the subject's healthcare provider, if the subject chooses to share this information.
- The site will complete the appropriate CRF page and this will mark the completion of the subject's participation in the study.

6.0 TREATMENT OF SUBJECTS

All vaccines associated with this study are to be stored separately from other vaccines and medications in a secure location under appropriate storage conditions with temperature monitoring. **All vaccines associated with this study must be checked for expiration date prior to use. Expired vaccines must not be administered to subjects.**

6.1 Study Vaccine(s)

The term 'study vaccine' refers to those vaccines provided by the Sponsor, which will be evaluated as part of the study objectives. The study vaccines specific to this study are described in Table 6.1-1.

Table 6.1-1: Study Vaccine Composition

Group A (Control) Meningococcal C-CRM$_{197}$ Conjugate Vaccine	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM$_{197}$ protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
Sodium Chloride	3.5 mg
Sterile water for injection, up to	0.5 ml

Group B (12.5µg LHD153R) - MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM$_{197}$ protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide/LHD153R Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
LHD153R	12.5 µg
Sodium Chloride	3.4 mg

Histidine	0.1 mg
Tris	30 µg
Sterile water for injection, up to	0.5 ml
Group C (25 µg LHD153R) - MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM$_{197}$ protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide/LHD153R Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
LHD153R	25 µg
Sodium Chloride	3.4 mg
Histidine	0.2 mg
Tris	61 µg
Sterile water for injection, up to	0.5 ml

Group D (50µg LHD153R) - MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM$_{197}$ protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg

Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide/LHD153R Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
LHD153R	50 µg
Sodium Chloride	3.2 mg
Histidine	0.4 mg
Tris	121 µg
Sterile water for injection, up to	0.5 ml
Group E (100µg LHD153R) - MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM$_{197}$ protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide/LHD153R Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
LHD153R	100 µg
Sodium Chloride	2.9 mg
Histidine	0.8 mg
Tris	243 µg
Sterile water for injection, up to	0.5 ml

6.2 Non-Study Vaccines

The term 'non-study vaccine' refers to those vaccines which will be intentionally given to study subjects but not formally included in the analysis of study objectives.

No non-study vaccines are planned for this study. Any non-study vaccines administered during the study conduct will be captured in the CRF as concomitant medications and/or vaccinations.

6.3 Vaccine Preparation and Administration

The investigator or designee will be responsible for oversight of the administration of vaccine to subjects enrolled in the study according to the procedures stipulated in this study protocol. All vaccines will be administered only by unblinded personnel who are qualified to perform that function under applicable local laws and regulations for the specific study site.

The vaccine components will be provided in 5 separate kits (i.e. one for the control and one for each of the 4 dosage groups). The vaccine components must be mixed prior to vaccination taking into account the appropriate aseptic procedures. Detailed vaccine preparation and administration instructions, including the maximal administration period, will be provided to investigators prior to study start and must be filed in the Investigator Site File.

PRECAUTIONS TO BE OBSERVED IN ADMINISTERING STUDY VACCINE:

- Prior to vaccination, subjects must be determined to be eligible for study vaccination and it must be clinically appropriate in the judgment of the investigator to vaccinate. Eligibility for vaccination prior to first study vaccine administration is determined by evaluating the entry criteria outlined in protocol sections 4.0.

- Study vaccines must not be administered to individuals with known hypersensitivity to any component of the vaccines.

- Standard immunization practices are to be observed and care should be taken to administer the injection intramuscularly. Before administering vaccine, the vaccination site is to be disinfected with a skin disinfectant (e.g., 70% alcohol). Allow the skin to dry. **DO NOT inject intravascularly**.

- As with all injectable vaccines, trained medical personnel and appropriate medical treatment must be readily available in case of anaphylactic reactions following vaccine administration. For example, epinephrine 1:1000, diphenhydramine, and/or other medications for treating anaphylaxis should be available.

6.4 Vaccine Administration Error or Overdose of Vaccine

Vaccine administration error is defined as receiving a dose of study vaccine that was not reconstituted as instructed or administered by a different route from the intended route of administration. An overdose of study vaccine (whether accidental or intentional) is defined when a dosage higher than the recommended dosage is administered in one dose of study vaccine.

Any vaccine administration error or overdose of study vaccine detailed in this protocol must be reported as an adverse event, and if the vaccine administration error or overdose is associated with a serious adverse event, it must be reported as such within 24 hours to the Sponsor.

6.5 Prior and Concomitant Medications and Vaccines

All medications, vaccines and blood products taken or received by the subject within 180 days prior to the start of the study are to be recorded in the appropriate CRF.

Medications taken for prophylaxis are those intended to prevent the onset of symptoms. Medications taken for treatment are intended to reduce or eliminate the presence of symptoms that are present.

NOTE: Use of antipyretics/analgesics within 24 hours prior to vaccine administration is a reason to delay study vaccination (see section 4.3).

Concomitant medications include all medications (including vaccines) taken by/administered to the subject at and after enrolment and must be documented in the appropriate CRF.

When recording concomitant medications/vaccines, they should be checked against the study entry criteria in section 4.0, to ensure that the subject should be enrolled in the study.

6.6 Vaccine Supply, Labeling, Storage and Tracking

The Sponsor will ensure the following:

- Supply the study vaccines.
- Appropriate labeling of all study vaccines provided that complies with the legal requirements of each country where the study is to be performed.

The investigator must ensure the following:

- Acknowledge receipt of the study vaccines by a designated staff member at the site, including:
  - Confirmation that the vaccines were received in good condition
  - Confirmation to the Sponsor of the temperature range during shipment from the Sponsor to the investigator's designated storage location
  - Confirmation by the Sponsor that the vaccines are authorized for use.
- Proper storage of the study vaccines, including:
  - Storage in a secure, locked, temperature-controlled location.
  - Proper storage according to the instructions specified on the labels.
  - Appropriate record keeping and inventory of the study vaccines, including regular documentation of adequate storage temperature.
- Appropriate use of the study vaccines, including:
  - No use of vaccines prior to receipt of authorization for use from the Sponsor.
  - Use only in accordance with the approved protocol.
  - Proper handling, including confirmation that the vaccine has not expired prior to administration.
  - Appropriate documentation of administration of vaccines to study subjects including:
    - Date, dosage, batch/lot numbers, expiration dates, unique identifying numbers assigned to subjects and study vaccines, and time of vaccine administration. This information will be maintained in an accountability log that will be reviewed by the site monitor.
    - Reconciliation of all vaccines received from the Sponsor. Reconciliation is defined as maintaining records of which and how many vaccines were received, which vaccines were administered to subjects, which vaccines were destroyed at the site, and which vaccines were returned to the Sponsor, as applicable.
- Proper adherence to the local institutional policy with respect to destruction of study vaccines.

- Complete record keeping of vaccine use, wastage, return or destruction, including documentation of:
  - Copy of the site's procedure for destruction of hazardous material.
  - Number of doses destroyed, date of destruction, destruction code (if available), method of destruction, and name of individual performing destruction.

Vaccines that have been stored differently from the manufacturer's indications **must not** be used unless the Sponsor provides written authorization for use. In the event that the use cannot be authorized, the Sponsor will make every effort to replace the vaccine supply. All vaccines used in conjunction with this protocol must be stored separately from normal hospital/practice stocks to prevent unintentional use of study vaccines outside of the clinical study setting.

Monitoring of vaccine accountability will be performed by the study monitor during site visits and at the completion of the study.

At the conclusion of the study, and as appropriate during the course of the study, the investigator must ensure that all unused study vaccines, packaging and supplementary labels are destroyed locally (upon approval from Sponsor) or returned to the Sponsor.

7.0 ASSESSMENTS

7.1 Safety Assessment

The measures of safety used in this study are based on previous study data and based on comparable routine clinical/laboratory procedures. They include a close vigilance for, and stringent reporting of selected local and systemic adverse events routinely monitored in vaccine studies as indicators of reactogenicity.

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

The period of observation for AEs extends from the time the subject signs informed consent until he or she completes the specified safety follow-up period (Day 366) or terminates the study early (whichever comes first). AEs occurring after the informed consent form is signed but prior to receiving study vaccine/product will be documented as an adverse event and recorded within the source documents. However, any AEs occurring prior to receipt of any study vaccine will be analyzed separately from “treatment emergent” AEs (AEs occurring after administration of the first study vaccine).

Adverse events are collected as either solicited or unsolicited adverse events. Solicited events are derived from organized data collection systems, such as Subject Diaries or interview.

7.1.1 Solicited Adverse Events

The term “reactogenicity” refers to solicited signs and symptoms (“solicited adverse events”) occurring in the hours and days following a vaccination, to be collected by the subject after the first 24 hours inpatient observation period at Day 1until Day 14, using a pre-defined Subject Diary.

The following solicited adverse events are included in the Subject Diary. Each adverse event is to be assessed using the scoring system shown in Appendix A (Solicited Local AEs) and Appendix B (Solicited Systemic AE):

Solicited Local Adverse Events

Solicited local AEs include:

- injection site erythema
- injection site induration
- injection site pain
- injection site swelling **Solicited Systemic Adverse Events**

Solicited systemic AEs include:

- body temperature ≥38.0°C (as measured orally)
- loss of appetite
- nausea
- fatigue
- generalized myalgia
- generalized arthralgia
- headache - chills
- vomiting
- diarrhea
- generalized rash
- urticaria

Other Solicited Data

Other solicited data collected per Subject Diary include:

- Use of analgesics/antipyretics recorded as “absent” or “present” and summarized by “for treatment” or “for prophylaxis”
- Body temperature as recorded daily, ideally at same time, by the oral route

The study staff must review the data entered into the Subject Diary as described in sections 3.4.2 and 5.3.1.

NOTE: Any solicited adverse event that meets any of the following criteria must be entered into the subjects' source documents (see section 9.1) and also as an adverse event in the appropriate CRF:

- Solicited local or systemic adverse event that continues beyond Day 14 after vaccination.
- Solicited local or systemic adverse event that leads to a visit to a healthcare provider (medically attended adverse event, see section 7.1.3).
- Solicited local or systemic adverse event leading to the subject withdrawing from the study or the subject being withdrawn from the study by the investigator (adverse event leading to withdrawal, see section 7.1.3).
- Solicited local or systemic adverse event that otherwise meets the definition of a serious adverse event (see section 7.1.4).

7.1.2 Unsolicited Adverse Events

An unsolicited adverse event is an adverse event that was not solicited using a Subject Diary and that was spontaneously communicated by a subject who has signed the informed consent.

7.1.3 Evaluation of Adverse Events

Every effort should be made by the investigator to evaluate safety information reported by a subject for an underlying diagnosis and to capture this diagnosis as the event in the AE page. In other words, the practice of reporting only symptoms (e.g., "cough" or "ear pain") are better reported according to the underlying cause (e.g., "asthma exacerbation" or "otitis media").

The severity of events reported on the appropriate CRF page will be determined by the investigator as:

Mild: transient with no limitation in normal daily activity.
Moderate: some limitation in normal daily activity.
Severe: unable to perform normal daily activity.

The relationship of the study treatment to an AE will be determined by the investigator based on the following definitions:

1. Not Related

The AE is not related to an investigational vaccine if there is evidence that clearly indicates an alternative explanation. If the subject has not received the vaccine, the timing of the exposure to the vaccine and the onset of the AE are not reasonably related in time, or other facts, evidence or arguments exist that reasonably suggest an alternative explanation, then the AE is not related.

2. Possibly Related

The administration of the investigational vaccine and AE are considered reasonably related in time and the AE could be explained by exposure to the investigational vaccine or by other causes.

3. Probably Related

Exposure to the investigational vaccine and AE are reasonably related in time and no alternative explanation has been identified.

The relationship of the study treatment to an unsolicited AE will be determined by the investigator.

Note: solicited AEs will not be evaluated for relationship to study treatment. Grading for severity of solicited local and systemic AEs is described in Appendix A and Appendix B.

Adverse events will also be evaluated by the investigator for the co-existence of any of the other following conditions:

- "Medically attended adverse event": an adverse event that leads to a visit to a healthcare provider.
- "New onset of chronic disease" (NOCD): an adverse event that represents a new diagnosis of a chronic medical condition that was not present or suspected in a subject prior to study enrolment.
- AEs leading to withdrawal: adverse events leading to study or vaccine withdrawal.

All AEs, regardless of severity, will be monitored until resolution or until the investigator assesses them as chronic or stable. All subjects experiencing AEs - whether considered associated with the use of the study vaccine or not - must be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible.

7.1.4 Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose results in one or more of the following:

- Death.
- Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe.
- Required or prolonged hospitalization.
- Persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions).
- Congenital anomaly/or birth defect.
- An important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

Adverse events which do not fall into these categories are defined as non-serious.

It should be noted that a severe adverse event need not be serious in nature and that a serious adverse event need not, by definition, be severe.

Serious adverse events will be captured both on the Vaccines Serious Adverse Event (VSAE) form as well as on the appropriate CRF page. All SAEs will be evaluated by the investigator for relationship of the event to study vaccine. SAEs that are judged to be possibly or probably related to the study vaccine should be reported to the Sponsor as related/suspected events.

The relationship of the study treatment to an SAE will be determined by the investigator based on the following definitions:

1. Related/suspected

The SAE is judged by the investigator to be possibly or probably related to the study vaccine on the appropriate CRF page (see section 7.1.3).

2. Not Related

The SAE is not related if exposure to the study vaccine has not occurred, **or** the occurrence of the SAE is not reasonably related in time, **or** the SAE is considered unlikely to be related to use of the study vaccine, i.e., there are no facts (evidence) or arguments to suggest a causal relationship.

The relationship of the study vaccine to an SAE will be determined by the investigator.

In addition, SAEs will be evaluated by the Sponsor or designee for "expectedness." An unexpected AE is one that is not listed in the current Summary of Product Characteristics or the Investigator's Brochure or an event that is by nature more specific or more severe than a listed event.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the appropriate CRF. If the onset of an event occurred before the subject entered the study (e.g., any pre-planned hospitalization for conditions like cosmetic treatments or for non-emergency routine visits for a pre-existing condition), the hospitalization would not lead to an AE being classified as serious unless, in the view of the investigator, hospitalization was prolonged as a result of participation in the clinical study or was necessary due to a worsening of the pre-existing condition.

7.1.4.1 Adverse Events of Special Interest

Certain adverse events of special interest (AESIs) are monitored after the administration of immunostimulatory agents. All subjects enrolled in this study will be monitored for AESIs for the entire follow-up period. The AESIs will be defined according to MedDRA preferred terms. The investigator will be provided with a list of AESIs prior to study start. Receipt of this list will be notified and stored, along with the list of AESIs, in the Investigator Site File. During the course of the trial the list of AESIs may change. If this occurs, the investigators will be advised of the change and confirmation of receipt will be documented. The updated list of AESIs and documentation of receipt are also stored in the Investigator Site File. The occurrence of any of these adverse events will be treated as a serious adverse event (SAE), meeting the criterion of a "medically important event."

Subjects will be assessed for diagnosis of an AESI at the following visits:

- Pre-vaccination clinic visit (Day -28 to Day -3)
- Visit 1 (Day 1, pre-vaccination)
- Visit 2 (Day 4)

- Visit 3 (Day 8)
- Visit 4 (Day 15)
- Visit 5 (Day 22; Safety Follow-Up Call) - Visit 6 (Day 29)
- Visit 7 (Day 85)
- Visit 8 (Day 113)
- Visit 9 (Day 181)
- Visit 10 (Day 209; Safety Follow-Up Call)
- Visit 11 (Day 271; Safety Follow-Up Call)
- Visit 12 (Day 366; Study Termination Visit)

At these visits a qualified health care practitioner listed on the site's responsibilities and delegation logs will conduct a review of organ systems and a targeted physical exam and will evaluate subjects for any new signs or symptoms that could indicate one of the AESIs as specified in the list of AESIs stored in the Investigator Site File. They will also interview the subject about recent medical history and any new diagnosis that could indicate an AESI. Medical records related to any new medical event or diagnosis will be requested, reviewed by the site staff, and recorded in the subject's source documents.

A diagnosis of an AESI will be reported in the same manner and time frame as an SAE using the VSAE form. The investigator must notify GSK within 24 hours. The AESI diagnosis, as well as any medications taken to treat the condition, will be recorded in the subject's source documents and on the appropriate CRF.

7.1.5 Methods for Recording Adverse Events and Serious Adverse Events

All findings regarding Adverse Events must be reported on the appropriate CRF page and on the VSAE form, if applicable, which is part of the Investigator Site File. All findings in subjects experiencing AEs must be reported also in the subject's source document.

All SAEs which occur during the course of the study, whether considered to be associated with the study vaccination or not, must be reported **within 24 hours of the site becoming aware of the event** to GSK or its designee. Specific instructions and contact details for collecting and reporting SAEs to GSK will be provided to the investigator.

All SAEs are also to be documented on the appropriate CRF page. Any medication or other therapeutic measures used to treat the AE will be recorded on the appropriate CRF(s) in addition to the outcome of the AE.

After receipt of the initial report, representatives of GSK or its designee will contact the investigator if it is necessary to obtain further information for assessment of the event.

All SAEs must be reported by the investigator to his/her corresponding EC and applicable regulatory authorities in accordance with institutional policy/regulatory requirements and adequate documentation of this notification must be provided to the Sponsor.

GSK or its designee must also comply with the applicable regulatory requirement(s) related to the reporting of suspected unexpected serious adverse vaccine reactions (also known as SUSARs) to the regulatory authority(ies) and the IRB/EC. If a SUSAR or other safety signal relating to use of one of the study vaccines is reported to GSK or its designee, the Sponsor will communicate the information to the investigator and the investigator will be responsible for submitting this information to the EC and other relevant authorities.

7.1.5.1 Post-Study Events

Any suspected SAE that occurs outside of the protocol-specified follow-up period or after the end of the study but considered to be caused by the study vaccine must be reported to GSK or its designee. These SAEs will be processed by GSK or its designee as during the course of the study, until 3 months after the last scheduled study visit. Instructions and contact details for collecting and reporting these suspected SAEs will be provided to the investigator.

7.1.6 Pregnancies

To ensure subjects' safety, each pregnancy in a subject after study vaccination must be reported to GSK within 72 hours of the site learning of its occurrence. If the subject agrees to submit this information, the pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if intended duration of safety follow-up for the study has ended.

Pregnancy data must be recorded on a Pregnancy Report CRF (initial report) and Pregnancy Follow-Up CRF (outcome report).

Any pregnancy outcome meeting the definition of a SAE (see section 7.1.4) must also be reported on the VSAE Report Form.

7.1.7 Safety Laboratory Measurements

Blood and urine samples will be collected from all subjects at the Pre-vaccination Screening, at Visit 1 (pre-vaccination and 24 hours after vaccination), at Visit 3 and at Visit 6 as outlined in Time and Events Table 3. The blood safety laboratory assessments will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, liver function tests (ALT, AST), a complete blood count and C-reactive protein. The urine safety laboratory assessments will include protein, glucose and red blood cells. An additional blood and urine sample will be collected in case of a clinic Early Termination Visit as outlined in section 5.5.1.

All testing will be conducted by qualified and certified laboratories. The Investigator **must** assess all safety laboratory results. Abnormal laboratory values must be classified by the Investigator as clinically significant or not. Abnormal laboratory values that are considered clinical significant will be defined following the FDA CBER Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" dated September 2007, or the institution's normal ranges if they differ from CBER guidance. Please see Appendix C, D and E for further details on the Toxicity Grading Scales according to CBER.

Retesting may be performed in case of abnormal values per guidance of the investigator.

7.2 Efficacy Assessment

Efficacy measurement will not be performed as part of this study.

7.3 Immunogenicity Assessment

The measures to assess the primary and secondary immunogenicity endpoints for this study are standard, i.e., widely used and generally recognized as reliable, accurate, and relevant (able to describe the quality and extent of the immune response).

The assay's used in this study to assess the primary and immunogenicity endpoints are human serum bactericidal assay (hSBA) and ELISA specific for MenC

The hSBA is a functional measure of the ability of specific antibodies, in conjunction with human complement, to kill MenC indicator strains, and is widely used and generally recognized as the serological correlate of protection. The specific ELISA will be used to measure the induction of antibodies directed against MenC following vaccination with the study vaccines.

Blood samples (approximately 10 ml) to obtain serum for hSBA and ELISA assays will be collected at Day 1, Day 8, Day 29 and Day 181 (refer to section 3.5 for detailed specimen collection procedures).

Testing will be conducted by a GSK or designated laboratory in a blinded manner towards the treatment group. Laboratory contact details are listed in the Protocol Ancillary Document.

All data will be captured at the laboratory and transferred via Electronic Data Transfer (EDT)

Details on all blood sample handling steps are described in the Clinical Specimen Lab Manual provided to the study site.

7.4 Exploratory Measurements

In those subjects who agree to a separate Informed Consent, additional blood samples will be collected at Day 1, Day 4, Day 8, Day 29 and Day 181 for exploratory measurements. The purpose of these exploratory measurements is to assess the systemic exposure of LHD153, to further delineate vaccine induced antigen specific immune responses and to evaluate biomarkers that may be predictive for safety and/or innate immune activation.

All exploratory measurements will be conducted by a GSK or a designated laboratory. Laboratory contact details are listed in the Protocol Ancillary Document.

Exploratory measurements may be performed after the Clinical Study Report (CSR) has been completed, in which case these data will be submitted as an addendum to the CSR.

Systemic exposure of LHD153

Systemic exposure of LHD153 will be assessed by analyzing LHD153 blood plasma levels at Day 1 (baseline, 1, 2, 4, 8 and 24h after vaccination) and Day 4 using LC/MS/MS. Time-points for assessment of clinical exposure of LHD153 have been selected based on non-clinical data in dogs and rats.

Vaccine-induced antigen-specific immune responses

The frequency of B cells specific for MenC polysaccharide and CRM_{197} will be determined by enzyme-linked immunosorbent spot (ELISPOT) at Day 1, Day 8, Day 29 and Day 181 in order to evaluate the baseline specific B-cell frequency (Day 1), the peak of plasmablast responses (Day 8), the peak of B cell memory responses (Day 29), and the persistence of memory B cell responses (Day 181).

Subsequently, the diversity of the antigen specific B-cell repertoire will be analyzed in a selected subset of subjects. The selection of the subset will be based on the most pronounced response to the study vaccines when compared to baseline as determined by the primary and secondary immunogenicity assessment.

The diversity of the elicited B-cell receptors will be assessed through sequence analysis of complementary DNA (cDNA) generated from immunoglobulin (Ig) messenger RNA (mRNA). The Ig cDNAs will be analyzed from antigen-specific B cells obtained at Day 1, Day 29 and/or Day 181 and plasmablasts isolated at Day 8. The analysis of the B-cell receptor diversity does not have the intent nor the capability to identify or rule out any genetic modifications in the RNA or DNA that are presumably linked to disease or predisposition to disease.

The frequency of T cells specific for the CRM_{197} protein at baseline (Day 1), at Day 8 and at Day 29 after vaccination with the study vaccines will be determined by FACS analysis using intracellular staining with a panel of cytokines and surface markers to identify cell populations.

Early Markers for Safety and Innate immune activation

The evaluation of potential biomarkers of safety and innate immune activation will be performed on blood specimens collected at Day 1 (baseline, 6h and 24h after vaccination) and Day 4.

The vaccine-induced production of inflammatory cytokines and chemokines will be monitored on serum samples using a commercially available electrochemoluminescence assay for a panel of pro-inflammatory cytokines and chemokines, including Eotaxin, Eotaxin-3, GM-CSF, IFN-g, IL-1a, IL-1b, IL-10, IL-12 p70, IL-12/IL-23p40, IL-13, IL15, IL-16, IL-17A, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-8 (HA), IP-10, MCP-1, MCP-4, MDC, MIP-1a, MIP-1b, TARC, TNF-a, TNF-b, VEGF.

The vaccine-induced expression of genes and gene families will be monitored on whole blood samples using of RNA microarrays by existing technologies. The RNA micro array analysis does not have the intent nor the capability to identify or rule out any genetic modifications in the RNA or DNA that are presumably linked to disease or predisposition to disease.

The vaccine-induced changes in myeloid (e.g. monocytes and dendritic cells) and lymphoid (e.g. NK cells, NKT cells) cell numbers and their activation status will be assessed using flow cytometry.

8.0 STATISTICAL CONSIDERATIONS

8.1 Endpoints

8.1.1 Primary Endpoint(s)

8.1.1.1 Primary Safety Endpoint(s)

The measures for assessing safety and tolerability (by vaccine group within each cohort and by LHD153R adjuvant dosage group overall) are as follows:

- The frequency and percentage of subjects with solicited local and systemic AEs through Day 14. Time intervals after vaccination that will be summarized are:30 minutes post-vaccination, Days 1-4 (without 30 minutes), Days 5-8, Days 8-14, Days 1-8 (without 30 minutes) and Days 1-14 (without 30 minutes).
- The frequency and percentage of subjects with any unsolicited AEs from the day of vaccination (Day 1) to Day 14.
- The frequency and percentage of subjects with SAEs, medically attended AEs, AEs leading to study withdrawal, NOCDs, AESIs for the following time periods: day of signed informed consent until study completion (Day 366), day of vaccination (Day 1) to Day 29, and Day 29 to study completion (Day 366).
- The absolute values and changes in hematology, chemistry, and urinalysis parameters (see section 7.1.7).
- The frequency and percentage of subjects with abnormal laboratory parameter values

as classified by investigator normal ranges (low, normal, high) and as classified by CBER toxicity grading scales, when available. **8.1.1.2 Primary Efficacy Endpoint(s)**

Not applicable.

8.1.1.3 Primary Immunogenicity Endpoint(s)

The primary immunogenicity endpoints are the GMTs measured by hSBA directed against MenC from samples collected on Day 1 (baseline, before vaccination) and Day 29 as well as the GMR of the titers (Day 29 / Day 1).

8.1.2 Secondary Endpoint(s) 8.1.2.1

Secondary Safety Endpoint(s)

Not applicable.

8.1.2.2 Secondary Efficacy Endpoint(s)

Not applicable.

8.1.2.3 Secondary Immunogenicity Endpoint(s)

The secondary immunogenicity endpoints are:

- GMTs and corresponding GMRs measured by hSBA directed against MenC for samples collected at Day 8 and Day181.
- Percentage of subjects with hSBA seroresponse at Days 8, 29, and 181. Seroresponse is defined as a post vaccination hSBA ≥8 for subjects with a baseline hSBA <4 or have an increase of at least 4 times the baseline hSBA level for subjects with prevaccination hSBA ≥4.
- Antibody geometric mean concentrations (GMCs) against MenC measured by ELISA for samples collected on Days 1 (baseline, prior to vaccination), 8, 29, and 181.
- The percentage of subjects with at least a 4-fold increase in antibody concentrations to MenC as measured by ELISA on Day 8, 29, and 181 relative to baseline (Day 1).

8.1.3 Exploratory Endpoint(s)

The exploratory endpoints are based on results of testing which may not be performed until after the study report has been finalized and will be further refined prior to testing. They include the following:

- Serum concentration of LHD153 at Day 1 baseline (prior to vaccination), Day 1 (1h , 2h, 4h, 8h, and 24h after vaccination), Day 4 by LC-MS/MS.
- Frequency of MenC polysaccharide-specific and CRM_{197}-specific B cells at Day 1 (baseline), Day 8, Day 29, and Day 181 by ELISPOT.
- Diversity of MenC polysaccharide-specific B-cell repertoire at Day 1 (baseline), Day 8, Day 29, and Day 181 by immunoglobulin cDNA sequencing.
- Frequency and quality of T cells specific for CRM_{197} at Day 1 (baseline), Day 8, and Day 29 by flow cytometry analysis using intracellular staining with a wide panel of cytokines and surface markers to identify cell populations.

- Serum concentrations of a panel of 30 chemokines and cytokines at Day 1 baseline (prior to vaccination), Day 1 (6h and 24h after vaccination), Day 4, and Day 8 by multiplex Electro-chemo-luminescence based assay.
- Gene expression profile in whole blood at Day 1 baseline (prior to vaccination), Day 1 (6h and 24h after vaccination), Day 4, and Day 8 by RNA micro array analysis.
- Number and activation status of myeloid and lymphoid cell populations at Day 1 baseline (prior to vaccination), Day 1 (24h after vaccination), Day 4 and Day 8 by flow cytometry.

8.2 Success Criteria

The study has no formal statistical hypotheses and will not be declared positive or negative according to given rules. The selection of an appropriate LHD153R adjuvant dosage for future studies will be determined by the joint evaluation of the immunogenicity and safety profiles of each dosage group. **8.2.1 Success Criteria for Primary Objective(s)** Not applicable.

8.2.2 Success Criteria for Secondary Objective(s)

Not applicable.

8.3 Analysis Sets

8.3.1 All Enrolled Set

All screened subjects who provide informed consent and provide demographic and/or baseline screening assessments, regardless of the subject's randomization and treatment status in the study and received a Subject ID.

8.3.2 All Exposed Set

All subjects in the enrolled set who receive a study vaccination.

8.3.3 Safety Set

Safety Set (solicited adverse events and other solicited reactions)

All subjects in the Exposed Set who:

- Provide post vaccination reactogenicity data.

Safety Set (unsolicited adverse events)

All subjects in the Exposed Set who:

- Have post-vaccination unsolicited adverse event records.

Safety Set (overall)

All subjects in the Exposed Set who:

- Have either post-vaccination adverse event or reactogenicity records.

Subjects will be analyzed as "treated" (i.e., according to the vaccine a subject received, rather than the vaccine to which the subject may have been randomized).

8.3.4 Full Analysis Set (FAS) Efficacy/Immunogenicity Set

All subjects in the Enrolled Set who:

- Receive a study vaccination AND provide efficacy/immunogenicity data at relevant time points.

FAS sets will be analyzed "as randomized" (i.e., according to the vaccine a subject was designated to receive, which may be different from the vaccine the subject actually received).

8.3.5 Per Protocol (PP) Set Efficacy/Immunogenicity Set

All subjects in the FAS efficacy/immunogenicity set who:

- Are not excluded due to reasons (see section 8.3.8) defined prior to unblinding or analysis.

PPS are subsets of FAS and should always be defined even if the objectives do not require it.

Examples for subjects excluded due to other reasons than protocol deviations are:

- Subjects who withdrew informed consent.
- Premature withdrawal due to an adverse event.

Exclusions need to be considered by objective/time point, i.e., sometimes not all data of a subject but only part of the subject's data will be removed from the PPS analysis.

8.3.6 Other Analysis Sets

All subjects in the Enrolled Set who consent to additional blood draws, receive a study vaccination AND provide exploratory assay data at relevant time points will be included in an exploratory assay subset.

8.3.7 Subgroups

Selected immunogenicity analyses may be provided based on seropositivity status at baseline.

8.3.8 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. A protocol deviation may be a reason to remove data from an analysis set at the time of analysis. Reportable protocol deviations will be defined as exclusionary from the analysis according to protocol objectives and endpoints, which will be specified in the Statistical Analysis Plan. In some cases exclusion of data may be due to a reason other than a protocol deviation, e.g. early termination.

8.4 Statistical Analysis Plan

This section provides a summary of the statistical methodology to be used. A more detailed description of analysis methods will be provided in a separate Statistical Analysis Plan which may also include additional exploratory analyses not explicitly mentioned in the following sections.

8.4.1 Analysis of Demographic and Baseline Characteristics

Descriptive statistics (number of non-missing observations, mean, standard deviation, median, minimum and maximum) for age, height and weight at enrolment will be calculated overall and by vaccine group and LHD153R adjuvant dosage.

Distributions of subjects by sex and ethnic origin will be summarized overall and by vaccine group and LHD153R adjuvant dosage.

8.4.2 Analysis of Primary Objective(s)

8.4.2.1 Analysis of Primary Safety Objective(s)

Safety of the study vaccines will be assessed in all subjects in terms of the frequency and percentage of reported AEs as well as by changes in clinical laboratory values.

8.4.2.1.1 Analysis of Extent of Exposure

The frequency and percentage of subjects with vaccinations will be summarized by vaccine group and LHD153R adjuvant dosage, by cohort and overall, for the Enrolled Set.

8.4.2.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events

All solicited adverse events will be summarized according to defined severity grading scales. Use of medication to prevent/treat fever will be summarized according to frequencies and percentages reporting “Yes” and “No”.

Frequencies and percentages of subjects experiencing each adverse event will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic adverse event overall and at each time point will also be presented.

Post-vaccination solicited adverse events reported from Day 1 to Day 14 will be summarized for the intervals Day 1-4 (without 30 minutes), Day 5-8, Day 1-8 (without 30 minutes), Day 8-14 and Day 1-14 (without 30 minutes) by maximal severity and by vaccine group and LHD153R adjuvant. The severity of solicited local adverse events, including injection-site erythema, swelling and induration will be summarized according to categories based on linear measurement: 25-50 mm, 51-100 mm, > 100 mm.

Injection site pain and systemic reactions (except fever) occurring up to Day 14 will be summarized according to “mild”, “moderate” or “severe”.

Each solicited local and systemic adverse event will also be further summarized as “none” versus “any”.

Implausible measurements (for further definition see Statistical Analysis Plan) will be left out of the analysis.

Use of antipyretics and analgesics will be summarized by frequency by type of use (prophylactic versus treatment) and percentage of subjects reporting use. The influence of antipyretics and analgesics use on the occurrence of specific adverse events (e.g., fever, pain) will be assessed.

Body temperature will be summarized by 0.5 °C and 1.0 °C increments from 36.0 °C up to ≥40 °C.

8.4.2.1.3 Analysis of Unsolicited Adverse Events

This analysis applies to all adverse events occurring during the study, judged either as probably related, possibly related, or not related to vaccination by the investigator, recorded in the CRF, with a start date on or after the date of first vaccination. AE starting prior to the first vaccination will only be listed. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class.

All reported adverse events, as well as adverse events judged by the investigator as at least possibly related to study vaccine, will be summarized according to system organ class and preferred term within system organ class. These summaries will be presented by vaccination group and LHD153R adjuvant dosage for each cohort and by interval of study observation. When an adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted.

Separate summaries will be produced for the following categories:

- Serious adverse events.
- Adverse events that are possibly or probably related to vaccine.
- Adverse events of special interest.
- New onset of chronic disease.
- Adverse event leading to withdrawal.
- Adverse events leading to a medically attended visit.
- Adverse event by data source.

Data listings of all adverse events will be provided by subject. In addition, adverse events in the categories above will be provided as listed data.

8.4.2.1.4 Analysis of Safety Laboratory Values

The investigator must review all safety laboratory results (see Section 7.1.7). Abnormal laboratory values and clinically significant changes in values from pre-vaccination (Screening Visit) will be assessed, using medical judgment, based on the FDA CBER Guidance for Industry “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials” dated September 2007, or the

institution's normal ranges if they differ from CBER guidance. Please see Appendix C, D and E for further details.

The following information will be provided:

- Change in absolute laboratory value from pre-vaccination (Screening Visit) and Day 1 (Visit 1) baseline to Day 1 (24 hours after vaccination), Day 8 (Visit 3) and Day 29 (Visit 6) after vaccination.
- The classification of laboratory values and/or their changes from pre-vaccination according to the CBER toxicity grading scale.
- 3 x 3 shift tables by visit using the categorization of laboratory values according to institutional normal reference ranges (below, within, above).

8.4.2.2 Analysis of Primary Efficacy Objective(s)

Not applicable.

8.4.2.3 Analysis of Primary Immunogenicity Objective(s)

8.4.2.3.1 Statistical Hypotheses

There are no statistical hypotheses associated with the primary immunogenicity objectives. All analyses are descriptive.

8.4.2.3.2 Analysis Sets

The primary immunogenicity analyses will be based on the per-protocol set (PPS) at Day 29. The primary analyses will be repeated using the Full Analysis Set (FAS) as a measure of the sensitivity/robustness of the results (further details are given in section 8.3).

8.4.2.3.3 Statistical Methods

Before any statistical analysis that assumes normally distributed observations, antibody titers will be $\log_{10}$-transformed. Individual titers below the limit of quantitation (LLQ) will be set to half that limit.

Geometric Mean Titers

The logarithmically (base 10) transformed antibody titers will be modeled using an analysis of covariance (ANCOVA) model with a qualitative factor for LHD153R adjuvant dosage (0 [for unadjuvanted MenC], 12.5, 25, 50 or 100 µg) and log (base 10)

pre-vaccination titer as a covariate. The adjusted GMT and the two-sided, 95%, confidence intervals (CIs) of the GMT will be calculated based on this model as will the ratio of GMTs and corresponding CIs. The adjusted GMT and two-sided 95% CIs will be constructed by exponentiation (base 10) of the least square means of the logarithmically transformed (base 10) antibody titer. The ratio of GMTs (LHD153R adjuvant dosage minus MenC), and corresponding two-sided 95% CIs, will be constructed by exponentiation (base 10) of the least square differences obtained from this model. The model can be written as:

$\log_{10}(y_{ik}) = \mu + \alpha_i + \beta x_{ik} + \varepsilon_{ik}$

where μ represents a common overall mean, α_i represents the adjuvant dose group i effect, β represents the common slope for the log10 pre-vaccination titer, x_{ik} for subject k in adjuvant dose group I, and ε_{ik} represents random error for subject k in adjuvant dose group i.

Geometric Mean Ratios

The logarithmically (base 10) transformed within subject ratio of antibody titers (Day 29 / pre-vaccination) will be modeled using an analysis of variance model with a qualitative factor for LHD153R adjuvant dosage (0 [for non-LHD153R adjuvanted MenC], 12.5, 25, 50 or 100 µg). The adjusted GMR and the two-sided, 95% CIs of the GMR will be calculated based on this model. The model can be written as:

$\log_{10}(y_{ik}) = \mu + \alpha_i + \varepsilon_{ik}$

where μ represents a common overall mean, α_i represents the adjuvant dose group i effect and ε_{ik} represents random error for subject k in adjuvant dose group i.

Handling of missing values

For immunogenicity data, it may be reasonable to consider missing immunogenicity values as missing completely at random (MCAR), i.e., not informative. Therefore, the primary analysis will comprise a complete case analysis only, without introducing any bias. Imputation methods will not be used.

8.4.3 Analysis of Secondary Objective(s) 8.4.3.1

Analysis of Secondary Safety Objective(s) Not

applicable.

8.4.3.2 Analysis of Secondary Efficacy Objective(s)

Not applicable.

8.4.3.3 Analysis of Secondary Immunogenicity Objective(s)

8.4.3.3.1 Statistical Hypotheses

There are no statistical hypotheses associated with the secondary immunogenicity objectives. All analyses are descriptive.

8.4.3.3.2 Analysis Sets

The secondary immunogenicity analyses will be based on the PPS (further details are given in section 8.3) or the appropriate subset of subjects.

8.4.3.3.3 Statistical Methods

The secondary immunogenicity endpoints are:

- GMTs and corresponding GMRs measured by hSBA directed against MenC for samples collected at Day 8 and Day181.
- Percentage of subjects with hSBA seroresponse at Days 8, 29, and 181. seroresponse is defined as a post vaccination hSBA ≥8 for subjects with a baseline hSBA <4 or have an increase of at least 4 times the baseline hSBA level for subjects with prevaccination hSBA ≥4.
- Antibody geometric mean concentrations (GMCs) against MenC measured by ELISA for samples collected on Days 1 (baseline, prior to vaccination), 8, 29, and 181.
- The percentage of subjects with at least a 4-fold increase in antibody concentrations to MenC as measured by ELISA on Day 8, 29, and 181 relative to baseline (Day 1).

The GMTs for samples collected at Day 8 and Day 181 as well as the GMCs for samples collected at Day 1, Day 8, Day 29, and Day 181 will be analyzed using the same approach as for the primary immunogenicity endpoint.

The remaining immunogenicity endpoints are based on subjects meeting criteria for seroconversion or achieving a certain threshold value. These endpoints will be summarized using frequencies and percentages by LHD153R adjuvant dosage (0 [for non-LHD153R adjuvanted MenC], 12.5, 25, 50 or 100 µg). Two-sided 95% ClopperPearson CIs will also be provided for percentages. For analyses of seroconversion, separate summaries may be provided based on seropositivity status at baseline.

8.4.4 Analysis of Exploratory Objectives

Testing and analyses of exploratory endpoints may be performed after the Clinical Study Report (CSR) has been completed, in which case these data will be submitted as an addendum to the CSR.

In general, concentration and titer results will be summarized for each LHD153R adjuvant dosage group using geometric means and associated 2-sided 95% confidence intervals; and, categorical data will be summarized using frequencies and percentages, with corresponding two-sided, 95% confidence intervals.

8.5 Sample Size and Power Considerations of Primary Objectives

Sample size is not driven by statistical assumptions for formal hypothesis testing, but was based on the safety objective for the study. The table below provides the probability for various combinations of sample size (N) and presumed true frequency of a given event within an individual vaccine group

Frequency of Event	Probability to Observe at Least 1 Subject with a Given Event For Various Choices of N			
	4	**8**	**12**	**16**
0.05	0.1855	0.3366	0.4596	0.5599
0.10	0.3439	0.5695	0.7176	0.8147
0.15	0.4780	0.7275	0.8577	0.9257
0.20	0.5904	0.8322	0.9313	0.9718
0.30	0.8250	0.9423	0.9862	0.9967
0.40	0.8704	0.9832	0.9978	0.9997

The proposed combinations of sample sizes within each cohort are 4 aluminium hydroxide adjuvanted MenC-CRM$_{197}$ and 16 MenC-CRM$_{197}$ plus an assigned-level of LHD153R adsorbed to aluminium hydroxide. If all four cohorts are fully enrolled, there will be 16 subjects receiving aluminium hydroxide adjuvanted MenC-CRM$_{197}$.

With 16 subjects, events which occur at a frequency of 15% or more will be detected with at least 90% probability; and, events which occur at a frequency of 10% or more will be detected with 81% probability. With 4 subjects, events which occur at a frequency of 30% or more will be detected with at least 80% probability. Intermediate values of 8 and 12

are provided to correspond to sample sizes in the MenC-CRM$_{197}$ after cohort 2 and cohort 3 are fully enrolled.

8.6 Interim Analysis

The DMC will be reviewing the accumulating safety data from the study in order to continue enrollment of subjects within a cohort and whether to enroll subjects into the next cohort.

In addition to these periodic reviews, there will be a safety and immunogenicity interim analysis for the selection of an LHD153R adjuvant dosage based on the data collected through Day 29 from subjects enrolled in all cohorts. This analysis will be performed by personnel not involved in study decisions. The results will be unblinded at the group level thereby preserving the blind for individual subjects. No adjustment to the overall alpha will be performed as the data collected subsequent to this analysis involve secondary and exploratory endpoints.

9.0 SOURCE DOCUMENTATION, STUDY MONITORING AND AUDITING

Study monitoring and auditing will be standardized and performed in accordance with the Sponsor's or delegated contract research organization's (CRO) standard operating procedures and applicable regulatory requirements (e.g., FDA, EMA, and ICH guidelines).

Prior to enrolment of the first study subject, GSK or delegate will train investigators and/or their study staff on the study protocol, all applicable study procedures, documentation practices and all electronic systems. CRFs must be completed for each enrolled subject (see section 8.3.1 for definition of enrolled subject). Documentation of screened but not enrolled subjects must be maintained at the site and made available for review by the site monitor.

9.1 Source Documentation

Prior to the start of the study, the site staff participating in the study conduct will be instructed on what documents will be required for review as source documents. The kinds of documents that will serve as source documents will be agreed between Sponsor or delegate and investigator and designees and specified in the SDA/Source Data Verification Form prior to subject enrolment.

In addition, source documentation **must** include all of the following: subject identification (on each page), eligibility and participation, proper informed consent procedures, dates of visits, adherence to protocol procedures, adequate reporting and follow-up of adverse events, documentation of prior/concomitant medication/vaccines, study vaccine receipt/dispensing/return records, study vaccine administration information, any data collected by a telephone conversation with the subject and date of completion and reason.

The subject must also allow access to the subject's medical records. Each subject must be informed of this prior to the start of the study and consent for access to medical records may be required in accordance with local regulations.

All safety data reported by subjects must be written down in source documents. If there are multiple sources of information (e.g., Subject Diary, verbal report of the subject, telephone contact details, medical chart) supporting the diagnosis of an adverse event, these sources must be identified in the source documents, discrepancies between sources clarified, the ultimate diagnosis must be justified and written in the source documents, and this diagnosis must be captured in the appropriate CRF page. The CRF must also

capture which source(s) of information were used to determine the adverse event (e.g., subject recall, medical chart, Subject Diary).

9.2 Study Monitoring, Auditing and Source Data Verification

Prior to enrolment of the first study subject, GSK or its designee (e.g., a CRO) will develop a Monitoring Plan to specify how centralized and/or on-site monitoring, including clinical specimens reconciliation, will be performed for the study. Study progress will be monitored as frequently as necessary to ensure:

- that the rights and well-being of human subjects are protected,
- the reported study data are accurate, complete, and verifiable from the source documents and
- the conduct of the study is in compliance with the current approved protocol/amendment(s), GCP and applicable regulatory requirements.

Contact details for the team involved in study monitoring will be provided to the investigator. Study data recorded on CRFs will be verified by checking the CRF entries against source documents in order to ensure data completeness and accuracy as required by study protocol.

Additional documents such as the investigator site file, pharmacy records, and informed consent documentation must also be available for review if requested. Arrangements for monitoring visits will be made in advance in accordance with the monitoring plan, except in case of emergency.

The investigator and/or site staff must make source documents of subjects enrolled in this study available for inspection at the time of each monitoring visit and Sponsor audits, when applicable. These documents must also be available for inspection, verification and copying, as required by regulations, by officials of the regulatory health authorities (e.g., FDA, EMA and others) and/or ECs/IRBs. The investigator and study site staff must comply with applicable privacy, data protection and medical confidentiality laws for use and disclosure of information related to the study and enrolled subjects.

10.0 DATA MANAGEMENT

10.1 Data Entry and Management

In this study, all clinical data (including, but not limited to, AE/SAEs, concomitant medications, medical history, and physical assessments), safety data, and immunogenicity data will be entered into an EDC system, which is compliant with Title 21 Part 11

policies of the Code of Federal Regulations (FDA, 1997). The data system includes password protection and internal quality checks. The EDC system will be designed and validated by the Sponsor prior to activation for data entry by sites. The investigator or designated delegate must review data entered and electronically sign the CRFs to verify their accuracy.

Access to the EDC system for data entry or review will require training and distinct individual access code assignments to those site staff members who will be entering study data and those involved in study oversight who may review study data. Data are collected within the EDC system, to which the Sponsor and site monitors have exclusively "read only" access.

Paper CRFs will be provided for each pregnant subject by the Sponsor. All appropriate pregnant subject data collected will be recorded on this form. One copy must be retained by the investigator, and all other copies (including the original copy) will be returned as directed by the Sponsor. Instructions on how to complete this form will be provided to the investigator.

10.2 Data Clarification

As part of the conduct of the trial, the Sponsor may have questions about the data entered by the site, referred to as queries. The monitors and the Sponsor are the only parties that can generate a query. All corrections and clarifications will be entered into the EDC system and will be identified by the person entering the information, the reason for the change, as well as the time of the changes made. If changes are made to a previously and electronically signed CRF, the investigator must confirm and endorse the changes

10.3 Data Protection

GSK respects the subjects' rights to privacy and will ensure the confidentiality of their medical information in accordance with all applicable laws and regulations.

The Sponsor as Data Controller according to the European Directive on the protection of individuals with regard to the processing of personal data and on the free movement of such data (95/46/EC) confirms herewith compliance to Directive 95/46/EC in all stages of Data Management.

11.0 RECORD RETENTION

Investigators must retain all study records required by GSK and by the applicable regulations in a secure and safe facility. The investigator must consult a GSK representative before disposal of any study records, and must notify the Sponsor of any change in the location, disposition, or custody of the study files. Essential documents must be retained for 15 years. “Essential documents” are defined as documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. These documents should be retained for a longer period, however, if required by the applicable national regulatory or institutional requirements.

These principles of record retention will also be applied to the storage of laboratory samples, provided that the integrity of the stored sample permits testing.

12.0 USE OF INFORMATION AND PUBLICATION

GSK assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov, and in compliance with current regulations.

GSK also assures that key results of this clinical study will be posted in a publicly accessible database within the required time-frame from the End of Study as defined in section 3.9.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

GSK must be notified of any intent to publish data collected from the study and prior approval from GSK must be obtained prior to submission for publication.

13.0 ETHICS

13.1 Regulatory and Ethical Compliance

The study will be conducted in compliance with the protocol, GCP and applicable regulatory requirement(s).

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, European Directive 2001/20/EC, GSK codes on protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki (European Council 2001, US Code of Federal Regulations, ICH 1997).

13.2 Informed Consent Procedures

Eligible subjects may only be included in the study after providing written informed consent or assent, as described in section 5.1.1. Before the start of the study, the investigator will have the informed consent and any other materials that will be provided to the subjects reviewed and approved by the IRB/EC. This review and approval will be documented and stored with other study documents. The investigator or designee must fully inform the subject or legal guardian of all pertinent aspects of the study. A copy of the written informed consent will be given to the subject or the designee. The subject/designee must be allowed ample time to ask about the details of the study and to make a decision as to whether or not to participate in the study. The subject and/or legal guardian(s) **must** sign the consent form indicating their agreement to participate in the study before any study-related procedures are conducted. The informed consent process may be conducted up to 28 days prior to vaccination on Day 1. If the subject is unable to read and write, a witness must be present during the informed consent discussion and at the time of informed consent signature.

Prior to the start of the study, GSK will provide to investigators a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by GSK before submission to the IRB/EC and a copy of the approved version must be provided to GSK after IRB/EC approval.

Women of childbearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements indicated in the protocol for the duration of the study. In case of doubt on

the ability of a subject to adhere to these requirements, that subject should not be allowed in the study

13.3 Responsibilities of the Investigator and IRB/EC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB/EC before study start. Properly constituted IRB/EC is defined in ICH Guideline for Good Clinical Practice E6 (R1), Section 3 (ICH, 1997). A signed and dated statement that the protocol and informed consent have been approved by the IRB/EC must be given to GSK before study initiation. Prior to study start and at any time the protocol is amended during study conduct, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to GSK monitors, auditors, GSK Clinical Quality Assurance representatives, designated agents of GSK, IRBs/ECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform GSK immediately that this request has been made.

The investigator also responsible for the following:

- Maintaining a list of appropriately qualified persons to whom the investigator has delegated significant study-related duties.
- Demonstrating the capability of recruiting the required number of suitable subjects within the recruitment period.
- Demonstrating sufficient time and staffing to properly conduct and complete the study within the agreed study period.
- Ensuring that all persons assisting with the study are adequately informed about the protocol, the investigational product(s), and their study-related duties and functions
- Ensuring that appropriately trained health care professionals are responsible for all study-related medical decisions and for ensuring appropriate medical care of subjects experiencing any adverse event related to the study.
- If permission to do so is given by the subject, ensuring that the subject's primary healthcare provider is informed of the subject's participation in the study.

The investigator should not implement any deviation from, or changes of the protocol without agreement by the Sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone

number(s)). In addition, the investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to study subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

(a) to the IRB/IEC for review and approval/favourable opinion,

(b) to the Sponsor for agreement and, if required,

(c) to the regulatory authority(ies).

13.4 Protocol Amendments

An amendment is a written description of change(s) to or formal clarification of a study protocol which may impact on the conduct of the clinical study, potential benefit of the clinical study, or may affect subject safety, including changes of study objectives, study design, subject population, sample sizes, study procedures, or significant administrative aspects. An administrative change of a study protocol is a minor correction or clarification that has no significant impact on the way the clinical study is to be conducted and no effect on subject safety (e.g., change of telephone number(s), logistical changes). Protocol amendments must be approved by GSK, health authorities where required, and the IRB/EC. In cases when the amendment is required in order to protect the subject safety, the amendment can be implemented prior to IRB/EC approval. Notwithstanding, the need for formal approval of a protocol amendment, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, GSK should be notified of this action, the IRB/EC at the study site, and, if required by local regulations, the relevant health authority should be informed within 10 working days.

14.0 REFERENCE LIST

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APPENDIX A: GRADING SCALES FOR SOLICITED LOCAL ADVERSE EVENTS*

(Adapted from CBER 2007b)

Adverse event Following Administration of Injectable Product	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Pain	present but does not interfere with activity	interferes with activity	prevents daily activity
Induration / Swelling / Erythema	25 – 50 mm	51 – 100 mm	> 100 mm

*This toxicity grading scale is adapted from CBER 2007 to enable ease of reporting by Subjects in the source documents for 'patient reported' solicited adverse events.. 'Grade 4' is not listed here but will be defined in the Statistical Analysis Plan as necessary.

APPENDIX B: GRADING SCALES FOR SOLICITED SYSTEMIC ADVERSE EVENTS*

(Adapted from CBER 2007b)

Systemic Adverse event		Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Fever	**°C**	38.0 – 38.4	38.5 – 38.9	39.0 – 40
	°F	100.4 – 101.1	101.2 - 102	102.1 - 104
Chills		present but does not interfere with activity	interferes with activity	prevents daily activity
Loss of Appetite		Loss of appetite without decreased oral intake	decreased oral intake without weight loss	decreased oral intake with weight loss
Nausea		Nausea present but not interfering with oral intake	Nausea leading to decreased oral intake	Nausea leading to minimal to no oral intake
Vomiting		1-2 episodes/24 hours	>2 episodes/24 hours	requires outpatient hydratation
Diarrhea		2-3 loose stools /24 hours	4-5 loose stools /24 hours	6 or more watery stools /24 hours or requires outpatient IV hydration
Generalized Myalgia		present but does not interfere with activity	interferes with activity	prevents daily activity
Generalized Arthralgia		present but does not interfere with activity	interferes with activity	prevents daily activity
Headache		present but does not interfere with activity	interferes with activity	prevents daily activity
Fatigue		present but does not interfere with activity	interferes with activity	prevents daily activity
Generalized Rash		localized area of the skin (1 extremity only)	moderate area of the skin (2 or more body regions without whole body involvement)	most of the skin
Urticaria		localized area of the skin (1 extremity only)	moderate area of the skin (2 or more body regions without whole body involvement)	most of the skin

*This toxicity grading scale is adapted from CBER 2007b to enable ease of reporting by Subjects in the source documents for 'patient reported' solicited adverse events. 'Grade 4' is not listed here but will be defined in the statistical analysis plan as necessary

APPENDIX C: TOXICITY SCALES FOR LABORATORY ABNORMALITIES (SERUM CLINICAL CHEMISTRY)

Serum*,**	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)***
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN

*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

**Laboratory values that fall in the normal range may be assigned a category of "Grade 0."

TOXICITY SCALES FOR LABORATORY ABNORMALITIES

***The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value. "ULN" = the upper limit of the normal range.

APPENDIX D:

(HEMATOLOGY)

Hematology*,*	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000

TOXICITY SCALES FOR LABORATORY ABNORMALITIES

Platelets Decreased cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000

*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
**Laboratory values that fall in the normal range may be assigned a category of "Grade 0."

APPENDIX E:

(URINE)

Urine*,**	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
**Laboratory values that fall in the normal range may be assigned a category of "Grade 0."

APPENDIX F: TOXICITY SCALES FOR VITAL SIGNS

Vital Signs*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Tachycardia - beats per minute	101-115	116-130	>130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute**	40-44	35-39	<35	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141-150	151-155	>155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91-95	96-100	>100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) mm Hg	85-89	80-84	<80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute***	21-23	24-27	>27	Intubation

*Subject should be at rest for all vital signs measurements
**Resting heart rate for young healthy subject population is between 45-90 per minute
***Respiratory rate for young healthy subject population is between 12-20 breaths per minute

Novartis

Document Approval Certificate /

PPD

The individuals listed have approved this document for implementation using an electronic signature in the
Atlas EDMS. PPD

UserName: PPD Title: Cluster Physician Date: Wednesday, 20 January 2016, 19:35 GMT
Meaning: As an approver, I agree with the content and format of this document.

This signature certificate is only valid when accompanied by all the pages of the document. /

CLINICAL STUDY PROTOCOL SPONSOR SIGNATURE PAGE

Study Number: V132_01EXP

Protocol Title: A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine in Healthy Adults (18-45 years of age)

Date of Final Issued Protocol and Version: 19 JAN 2016, Version 6

Signature page for sponsor's representative

The following sponsor's representative has reviewed and approved the protocol entitled "A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine in Healthy Adults (18-45 years of age)." In addition, this study protocol has been approved by the GSK Protocol Review Committee and received an electronic approval signature on 11 SEP 2015.

[redacted] 20 JAN 16

Cluster Physician, GSK Date, DD MMM YY

[redacted]

Printed Name of Cluster Physician, GSK

PPD

CLINICAL STUDY PROTOCOL V132_01EXP Version 7

A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine in Healthy Adults (18-45 years of age)

EUDRACT No. 2014-002430-31

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Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
GlaxoSmithKline Biologicals S.A.	V132_01EXP	MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and Meningococcal C-CRM$_{197}$ Conjugate Vaccine
Title of Study: A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine in Healthy Adults (18-45 years of age)		
Study Period: Approximately 12 months for each subject		**Clinical Phase:** Phase 1

Background and Rationale:

Neisseria meningitidis (*N. meningitides*) serogroup C (MenC) is one of the major serogroups causing invasive meningococcocal disease. Case fatality in Germany has ranged between 6% and 8% between 1999 and 2006, and has remained generally consistent across the different European countries, varying between 6-11%, with the case fatality rate being notably higher for serogroup C disease than for serogroup B. The safety and immunogenicity of the GSK Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) has been confirmed through years of commercial use. For children over the age of 12 months, for adolescents and for adults a single dose is recommended. For infants between 2 and 12 months of age, the recommended schedule for primary immunization with the Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) is two doses given with an interval of at least 2 months A more potent Meningococcal CCRM$_{197}$ Conjugate Vaccine formulation might enable a reduction of the antigen dosage and/or a reduction in the number of doses needed in infants. One approach to achieve more potent well-characterized sub-unit vaccines - like the Meningococcal C-CRM$_{197}$ Conjugate Vaccine - is the use of new adjuvants that activate the Toll-like receptor (TLR) pathway.

GSK is developing a small molecule immune potentiator (SMIP) LHD153 that is an agonist for TLR7. The objective driving the development of LHD153 is to achieve a vaccine adjuvant with strong immunopotentiating properties and minimal side effects. In line with this objective, it has been postulated that the ideal SMIP should remain local

and target innate immune cells at the injection site. To this end, LHD153 contains a functional phosphonate group to allow for adsorption to aluminium hydroxide. The

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
GlaxoSmithKline Biologicals S.A.	V132_01EXP	MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and Meningococcal C-CRM$_{197}$ Conjugate Vaccine

arginine salt derivative of this compound is LHD153R. Preclinical results from animal models for bacterial and viral antigens, including MenC, MenB, rabies, HIV and respiratory syncytial virus (RSV) showed increased functional antibodies and antigenspecific T-cells with LHD153R adsorbed to aluminium hydroxide (Aluminium Hydroxide/LHD153R) when compared to aluminium hydroxide adjuvanted controls. *In vitro* toxicity screens confirmed that LHD153R is not phototoxic, genotoxic or mutagenic. Furthermore, toxicology studies in dog and rats showed that intramuscular (IM) injection of Aluminium Hydroxide/LHD153R was well tolerated. Importantly, in contrast to free LHD153R, toxicokinetic analysis in rats and dogs confirmed very limited exposure of LHD153 when LHD153R was adsorbed to aluminium hydroxide after IM injection.

The aim of this Phase 1 clinical study is to assess the safety of Aluminium Hydroxide/LHD153R adjuvanted MenC-CRM_{197} conjugate vaccine (MenCCRM$_{197}$/Aluminium Hydroxide/LHD153R) and to compare the antibody-mediated immune response elicited by MenC-CRM_{197}/Aluminium Hydroxide/LHD153R with the licensed aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (Menjugate®). Furthermore, a comprehensive set of exploratory objectives has been selected to assess the systemic exposure of LHD153 after intramuscular injection of MenC-CRM_{197}/Aluminium Hydroxide/LHD153R, to evaluate the quality of the specific immune response against MenC-CRM_{197} in detail and to evaluate biomarkers that may be predictive of safety and/or innate immune activation.

The licensed Meningococcal C-CRM_{197} Conjugate Vaccine (Menjugate®) has been selected as the primary vaccine candidate to assess the safety and immunopotentiating properties of Aluminium Hydroxide/LHD153R for several reasons. Firstly, the safety and immunogenicity profiles of the Meningococcal C-CRM_{197} Conjugate Vaccine (Menjugate®) have been well established through years of commercial use. Secondly, a more potent MenC-CRM_{197} conjugate vaccine might enable a reduction of the antigen dosage or the number of doses needed in infants. Finally, MenC-CRM_{197} is a wellcharacterized, single conjugate antigen preparation which provides an ideal setting to evaluate the potential of this new Aluminium Hydroxide/LHD153R adjuvant.

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
GlaxoSmithKline Biologicals S.A.	V132_01EXP	MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and Meningococcal C-CRM$_{197}$ Conjugate Vaccine

Study Objectives:

Primary Safety Objective:

To assess the safety of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R as compared to that of aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine.

Primary Immunogenicity Objective:

To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine at Day 29, as measured by human complement serum bactericidal assay (hSBA) directed against MenC.

Secondary Immunogenicity Objectives:

1. To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal CCRM$_{197}$ Conjugate Vaccine, at Day 8 and Day 181 after vaccination, as measured by hSBA directed against MenC. Baseline antibody titers will also be measured by hSBA.
2. To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal CCRM$_{197}$ Conjugate Vaccine at Day 8, Day 29 and Day 181 after vaccination, as measured by an enzyme-linked immunosorbent assay (ELISA) to MenC. Baseline antibody concentrations will also be measured by ELISA.

Exploratory Objectives:

1. To evaluate the systemic exposure of LHD153 at several early time-points after IM injection of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R or aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine.
2. To explore the frequency of B cells specific for MenC polysaccharide and CRM$_{197}$ protein at baseline (Day 1) and at Day 8, Day 29 and Day 181 after vaccination with

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MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R or the aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine. Subsequently, the B cell repertoire of the antigen specific B cells will be analyzed in a selected subset of subjects.

3. To explore the baseline T cell mediated immunity to CRM$_{197}$ and to evaluate the frequency and quality of CRM$_{197}$ specific T cells induced by MenC-CRM$_{197}$/Aluminium Hydroxide/ LHD153R compared to aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine at Day 8 and Day 29.
4. To evaluate biomarkers that may be predictive for safety and/or innate immune activation.
5. ***To explore the biophysical and functional characteristics of antibodies induced by MenC-CRM197/Aluminium Hydroxide/LHD153R or aluminium hydroxide adjuvanted Meningococcal C-CRM197 Conjugate Vaccine. (Amended: 19 June 2017)***

Study Design:

This Phase 1, randomized, observer-blind, dosage-escalation study will be performed at a single center. In total, approximately 80 healthy male and healthy non-pregnant female adults (18-45 years of age) will be enrolled in the study. Subjects will be randomized to receive a single IM vaccination of either the licensed aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (i.e. 10 µg MenC conjugated to CRM_{197}, adjuvanted with 1 mg aluminium hydroxide) or one of four dosages of the investigational vaccine, MenC-CRM_{197}/Aluminium Hydroxide/LHD153R (i.e. 10 µg MenC conjugated to CRM_{197}, adjuvanted with 1 mg aluminium hydroxide and one of four dosages [12.5, 25, 50 or 100 µg] of LHD153R).

For the dosage-escalation of LHD153R, the subjects will be enrolled into 1 of 4 cohorts, in a stepwise manner with 20 subjects per cohort. Subjects in all cohorts will be randomized in a 1:4 ratio, to receive either aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (control) or MenC-CRM_{197}/Aluminium Hydroxide/LHD153R with increasing doses of LHD153R.Cohort 1 will receive 12.5 µg of LHD153R; Cohort 2 will receive 25 µg of LHD153R; Cohort 3 will receive 50 µg of

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LHD 153; and Cohort 4 will receive 100 µg of LHD153R (Table 1).

Table 1: Subjects Randomized per Cohort and Treatment Dosage Group

Cohort	Group	Subjects/ Group	MenC Dosage* (µg)	Adjuvant Dosages		Total Volume/Dose	Total Subjects/Cohort
				Aluminium Hydroxide (mg)	LHD153R (µg)		
1	A	4	10	1	0	0.5 mL	20
	B	16	10	1	12.5	0.5 mL	
2	A	4	10	1	0	0.5 mL	20
	C	16	10	1	25	0.5 mL	
3	A	4	10	1	0	0.5 mL	20
	D	16	10	1	50	0.5 mL	
4	A	4	10	1	0	0.5 mL	20
	E	16	10	1	100	0.5 mL	

*Conjugated to 12.5-25 µg CRM_{197}

After vaccination, all subjects will be confined to the clinical site for 24 hours for clinical observation, including but not limited to observations for solicited and unsolicited adverse events, body temperature measurements and blood sampling for exploratory endpoint measurements.

Importantly, all cohorts will have a staggered entry based on Data Monitoring Committee (DMC) reviews.

- For each cohort, the first 5 subjects (i.e. the first 1:4 randomization block) to receive either aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (n=1) or MenC-CRM_{197}/Aluminium Hydroxide/LHD153R (n=4) will be treated at a vaccination rate of 1 subject each day.
- After entry of the first 5 subjects in each cohort, the enrollment will be paused. The remaining 15 subjects for each cohort will be enrolled only after DMC review of the safety results obtained through Day 14 has been finalized (Table 2).
- In addition, enrollment of the first 5 subjects in the next cohort will only proceed after the Day 14 safety results of the first 5 subjects of the previous cohort have been reviewed by the DMC (Table 2).

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- Furthermore, all available Day 14 and Day 29 safety results will be included in DMC reviews between the different enrollment stages.

Table 2: Overview of staggered entry of subjects based on DMC reviews

Stage	Dosage Cohort	MenC-CRM$_{197}$/ Aluminium Hydroxide (n)	MenC-CRM$_{197}$/ Aluminium Hydroxide /LHD153R (n)
1	1	1	4
Enrollment pause until DMC review of Stage 1 Day 14 Safety Results			
2	1	3	12
	2	1	4
Enrollment pause until DMC review of Stage 1 Day 29 and Stage 2 Day 14 Safety Results			
3	2	3	12
	3	1	4
Enrollment pause until DMC review of Stage 2 Day 29 and Stage 3 Day 14 Safety Results			
4	3	3	12
	4	1	4
Enrollment pause until DMC review of Stage 3 Day 29 and Stage 4 Day 14 Safety Results			
5	4	3	12

The DMC review will be performed according to predefined stopping/pausing guidelines used to ensure the safety of study subjects. These stopping/pausing guidelines are based on FDA guidance and with grading scales from the CBER Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials". See protocol section 3.6 for further details.

Safety Measurements

Schedule of safety data collection:

- Solicited local and systemic adverse events (AEs), body temperature and all unsolicited AEs will be collected until Day 14.
- All serious adverse events (SAEs), medically attended AEs, AEs leading to study withdrawal, new onset of chronic disease (NOCDs), and adverse events of special interest (AESIs) will be collected from the date of signed informed consent to study

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completion at Day 366.

- All concomitant medications administered in relation to the reported AEs will be collected from vaccination to study completion at Day 366.

Solicited local AEs include injection site erythema, injection site induration, injection site pain and injection site swelling. Solicited systemic AEs include body temperature ≥ 38.0°C (as measured orally), loss of appetite, nausea, fatigue, generalized myalgia, generalized arthralgia, headache, chills, vomiting, diarrhea, generalized rash and urticaria.

All AESIs will be reported in the same manner as SAEs. All AEs will be monitored until resolution or, if the AE becomes chronic, a cause is identified. If an AE is unresolved at the conclusion of the study, a clinical assessment will be made by the investigator and the medical monitor to determine whether or not continued follow-up of the AE is warranted.

The relationship of the study treatment to any AE will be determined by the investigator as probably related, possibly related, or not related; the relationship of the study treatment to any SAE will be determined by the investigator as probably related/suspected, or not related.

Safety Laboratory Parameters

To assess laboratory AEs, blood and urine samples will be collected from each subject as outlined in Table 3 to perform blood chemistry, hematology, and urine analyses.

Safety laboratory samples will be drawn from all subjects at pre-vaccination screening (between Day -28 and Day -3) at Day 1 (pre-vaccination and 24h after vaccination), at Day 8 and at Day 29. Safety laboratory assessments will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, liver function tests (ALT, AST), a complete blood count and C-reactive protein. A urine sample will be collected at the same time-points and will be assessed for the presence of protein, glucose and red blood cells.

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Primary and Secondary Immunogenicity Measurements

Four blood samples per subject (i.e. at Day 1, Day 8, Day 29 and Day 181) will be collected for serum preparation and determination of antibody-mediated immune responses to MenC-CRM$_{197}$ as outlined in Table 3 and Table 4. See section 7.3 for further details.

Exploratory Measurements

In all subjects who agree by signing a separate Informed Consent, additional blood samples will be collected at Day 1, Day 4, Day 8, Day 29 and Day 181 for exploratory assays as outlined in Table 3 and Table 4. The purpose of these assays is to assess the systemic exposure of LHD153, to determine the frequency and quality of B- and T-cells specific for MenC polysaccharide and/or CRM$_{197}$ and to evaluate biomarkers that may be predictive of safety and/or innate immune activation. Subsequently, MenC-CRM$_{197}$ specific B-cell repertoires will be analyzed in a selected subset of subjects, dependent on the results from primary and secondary immunogenicity measurements and the volume of blood remaining for additional testing. See section 7.4 for further details. All exploratory analyses may be performed after the Clinical Study Report (CSR) has been completed, in which case these data will be submitted as an addendum to the CSR.

Number of Subjects planned:

Approximately 80 adult subjects will be randomized, with anticipated dropout rates of 5% by Day 181 (last serology time point), and 10%, by Day 366 (last safety time point).

Sample size is not driven by statistical assumptions for formal hypothesis testing, but the proposed number of subjects will be sufficient to provide a descriptive summary of the safety and immunogenicity of the study vaccine.

Study Population and Subject Characteristics:

Healthy adult male and female volunteers between 18-45 years of age, inclusive.

The list of inclusion and exclusion criteria is included in protocol section 4.0.

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Study Vaccines:

The MenC-CRM$_{197}$ conjugate is a lyophilized powder consisting of 10 µg of MenC polysaccharide conjugated to 12.5-25 µg CRM$_{197}$ carrier protein. The MenC-CRM$_{197}$ lyophilized powder will be reconstituted with adjuvant by the unblinded designated site staff member who is to follow the procedure as described in the vaccine preparation instructions in the Investigator Site File (i.e. the vaccine will be prepared in the clinic prior to administration).

The lyophilized MenC-CRM$_{197}$ powder will be reconstituted with either:

(a) aluminium hydroxide adjuvant

(b) Aluminium Hydroxide/LHD153R adjuvant with specified dosages of LHD153R (12.5, 25, 50 or 100 µg)

The components for each formulation of MenC-CRM$_{197}$ will be provided in a separate kit.

Aluminium Hydroxide/LHD153R with specified dosages of LHD153R will be prepared by dilution of the highest Aluminium Hydroxide/LHD153R dosage (100 µg of LHD153R) with aluminium hydroxide.

In each cohort, subjects will be randomized to receive one injection of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R adjuvant or aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine. The 0.5 mL of vaccine will be injected IM in the deltoid muscle, with preference that the injection is administered in the nondominant arm.

Primary Safety Endpoint:

Safety will be assessed by measuring the frequency of local and systemic solicited AEs, unsolicited AEs, SAEs, AESIs, NOCDs, and safety laboratory data for all subjects. Specifically,

- The frequency and percentage of subjects with solicited local and systemic AEs through Day 14. Time intervals after vaccination that will be summarized are: 30

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min post-vaccination, Days 1-4 (without 30 min), Days 5-8, Days 8-14, Days 1-8 (without 30 min) and Days 1-14 (without 30 min).

- The frequency and percentage of subjects with any unsolicited AEs from the day of vaccination (Day 1) to Day 14.
- The frequency and percentage of subjects with SAEs, medically attended AEs, AEs leading to study withdrawal, NOCDs, AESIs for the following time periods: day of signed informed consent until study completion (Day 366), day of vaccination (Day 1) to Day 29 and Day 29 to study completion (Day 366).
- The absolute values and changes in hematology, chemistry, and urinalysis parameters.
- The frequency and percentage of subjects with abnormal laboratory parameter values as classified by investigator normal ranges (low, normal, high) and as classified by CBER toxicity grading scales, when available.

Primary Immunogenicity Endpoint:

Geometric mean titers (GMTs) measured by hSBA directed against MenC from samples collected on Day 1 (baseline, before vaccination) and Day 29 as well as the GMR of the titers (Day 29 / Day 1).

Secondary Immunogenicity Endpoints:

- GMTs and corresponding GMRs measured by hSBA directed against MenC for samples collected at Day 8 and Day181.
- Percentage of subjects with hSBA seroresponse at Day 8, Day 29, and Day 181. seroresponse is defined as a post vaccination hSBA $\geq$8 for subjects with a baseline hSBA <4 or have an increase of at least 4 times the baseline hSBA level for subjects with pre-vaccination hSBA $\geq$4.
- Antibody geometric mean concentrations (GMCs) against MenC measured by ELISA for samples collected on Day 1 (baseline, prior to vaccination), Day 8, Day 29, and Day 181.
- The percentage of subjects with at least a 4-fold increase in antibody concentrations

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to MenC measured by ELISA on Day 8, Day 29, and Day 181 relative to baseline (Day 1).

Exploratory *Immunogenicity* Endpoints:

Testing and analyses of exploratory ***immunogenicity*** endpoints may be performed after the Clinical Study Report (CSR) has been completed, in which case these data will be submitted as an addendum to the CSR.

1. Serum concentration of LHD153 at Day 1 baseline (prior to vaccination), Day 1 (1h , 2h, 4h, 8h, and 24h after vaccination) and Day 4 by LC-MS/MS.
2. Frequency of MenC polysaccharide-specific and CRM$_{197}$-specific B cells at Day 1 (baseline), Day 8, Day 29, and Day 181 by ELISPOT.
3. Diversity of the MenC polysaccharide-specific B-cell repertoire at Day 1 (baseline), Day 8, Day 29, and Day 181 by immunoglobulin cDNA sequencing.
4. Frequency and quality of T cells specific for CRM$_{197}$ at Day 1 (baseline), Day 8, and Day 29 by flow cytometry using intracellular staining with a panel of cytokines and staining of surface markers to identify cell populations.
5. Serum concentrations of a panel of 30 chemokines and cytokines at Day 1 baseline (prior to vaccination), Day 1 (6h and 24h after vaccination), Day 4, and Day 8 by electrochemo-luminescence based assay.
6. Gene expression profile in whole blood at Day 1 baseline (prior to vaccination), Day 1 (6h and 24h after vaccination), Day 4, and Day 8 by RNA micro array analysis.
7. Number and activation status of myeloid and lymphoid cell populations at Day 1 baseline (prior to vaccination), Day 1 (24h after vaccination), Day 4 and Day 8 by flow cytometry.

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8. ***Antigen specific antibody isotype, Fc receptor binding capability and antibody glycosylation state will be assessed at Day 1 (baseline), Day 29, and Day 181.***
9. ***Functionality of MenC-specific antibodies to fix complement, promote antibodydependent cell mediated cytoxicity (ADCC), induce phagocytosis (ADCP) and activate FcR+ cells in vitro will be also assessed at Day 1 (baseline), Day 29, and Day 181.(Amended: 19 June 2017)***

Statistical Analyses:

The study is exploratory in nature, thus analyses will be descriptive and no formal hypothesis testing will be performed.

Primary Safety Analyses

The primary safety analyses will be based on the safety set for solicited and unsolicited adverse events. There is no statistical null hypothesis associated with the safety objective, which will be analyzed descriptively.

Immunogenicity Analyses

The primary immunogenicity analyses will be based on the per-protocol set (PPS) on Day 29. The primary analyses will also be performed using the Full Analysis Set (FAS) as a measure of the sensitivity/robustness of the results. All other immunogenicity assessments will be performed using the PPS or the appropriate subset of subjects. The antibody concentrations/titers will be summarized using GMC/GMTs and two-sided 95% confidence intervals (CIs) constructed by exponentiation (base 10) of the least square means of the logarithmically transformed (base 10) antibody titer. The 95% CIs will be obtained from an analysis of covariance (ANCOVA) with baseline concentration/titer as a covariate. Additional details will be further described in the Statistical Analysis Plan.

The immunogenicity endpoints based on subjects meeting criteria for seroconversion or achieving a certain threshold value will be summarized using frequencies and percentages and associated two-sided 95% Clopper-Pearson CIs. For analyses of seroconversion, separate summaries may be provided based on seropositivity status at

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baseline.		
Interim Analysis: An Interim Analysis will be performed on the immunogenicity and safety data collected from all subjects until Day 29, after all cohorts have been enrolled. Further details regarding the interim analysis are contained in section 8.6.		
Data Monitoring Committee: An independent DMC will be implemented to review safety data during scheduled periodic reviews. The DMC will review safety data collected until Day 14, as described in the DMC charter and in the Statistical Analysis Plan, after enrollment of the first 5 subjects in each cohort, before proceeding with enrollment of the remaining 15 subjects in each cohort. In addition, enrollment of the first 5 subjects of the next cohort will only proceed after the Day 14 safety results of the first 5 subjects of the previous cohort have been reviewed. Furthermore, all available Day 14 and Day 29 safety results will be included in DMC reviews between the different enrollment stages. Further information regarding the DMC is discussed in more detail in the protocol, section 3.7.		

Table 3: Time and Events Table – Treatment Period (until Day 29)

		Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit	Phone Call	Clinic Visit
	Visit Type	**-28 to -3**	**1**	**4**	**8**	**15**	**22**	**29**
	Study Day	**n/a**	**n/a**	**n/a**	**-1/+1**	**+1**	**n/a**	**-2/+2**
	Visit Window (Days)							
	Visit Number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**
Study Event	**References**							
Study Treatment								
Vaccination	Section 5.2		X					
Screening and Safety								
Informed Consent	Section 5.1.1	X						
Demographic Data & Medical History	Sections 5.1.2	X						
Physical Exam	Sections 5.1.2 and 5.2.1	X	X[a]					
Safety Laboratory blood draw (10 ml)	Section 7.1.7	X	X[b]		X			X
Urinalysis	Sections 7.1.7	X	X[b]		X			X
Pregnancy Test	Sections 5.1.2 and 5.2.1	X	X[a]					
Exclusion/Inclusion Criteria	Section 4.0	X	X[a]					
Randomization	Section 5.2.3		X[a]					

30 min and 24 hr Post Injection Assessment	Section 5.2.5		X_c					
Subject Diary Dispensed with Training	Section 5.2.5		X					
Subject Diary Reminder	Section 5.2.5			X	X			
Subject Diary Reviewed and Collected	Section 5.3.1					X		
Assess all solicited AEs	Section 7.1.1 and 7.1.3					X		
Assess all unsolicited AEs	Sections 7.1.2 and 7.1.3	X	X	X	X	X		

		Clinic Visit	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Phone Call**	**Clinic Visit**
	Visit Type	**-28 to -3**	**1**	**4**	**8**	**15**	**22**	**29**
	Study Day	**n/a**	**n/a**	**n/a**	**-1/+1**	**+1**	**n/a**	**-2/+2**
	Visit Window (Days)							
	Visit Number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**
Study Event	**References**							
Assess SAEs	Section 7.1.4	X	X	X	X	X	X	X
Assess AESIs	Section 7.1.4.1	X	X	X	X	X	X	X
Assess NOCDs, medically attended AEs, AEs leading to withdrawal	Sections 7.1.3	X	X	X	X	X	X	X
Assess relevant medications	Sections 5.1.2 and 6.5	X	X	X	X	X	X	X
Blood draws for Immunogenicity and Exploratory Objectives								
Serum Blood Draws (Primary/Secondary Objectives; 10 mL)	Section 3.5		X_a		X			X

Serum Blood Draws (Exploratory Objectives; 5 mL)	Section 3.5		Xd	X	X			
Whole Blood Draws (Exploratory Objectives; 3 mL)	Section 3.5		Xe	X				
Whole Blood Draws (Exploratory Objectives; 5 mL)	Section 3.5		Xf	X	X			
Whole Blood Draws (Exploratory Objectives; 20 mL)	Section 3.5		Xg	X				
Whole Blood Draws (Exploratory Objectives; 50 mL)	Section 3.5							X
Whole Blood Draws (Exploratory Objectives; 70 mL)	Section 3.5		Xa		X			

Notes:
a. Procedure must be performed prior to vaccination.
b. Two blood draws (2 x 10 ml) and two urine samples must be taken at Study Day 1, i.e. at baseline (prior to vaccination) and at 24h after vaccination.
c. Vital signs will be measured at 30 min and 24h. Additional body temperature measurement must be performed at 2, 4, 6, 8, 10, 12 and 18h after vaccination.
d. Three Serum Blood Draws (3 x 5ml) must be taken at Study Day 1, i.e. at baseline (prior to vaccination), at 6h and at 24h after vaccination.
e. Six Whole Blood Draws (6 x 3 mL) must be taken at Study Day 1, i.e. at baseline (prior to vaccination) and at 1, 2, 4, 8 and 24h after vaccination.
f. Three Whole Blood Draws (3 x 5 mL) must be taken at Study Day 1, i.e. at baseline (prior to vaccination), at 6h and at 24h after vaccination. g. Whole Blood Draw (20 mL) at Study Day 1 must be taken at 24h after vaccination.

Table 4: Time and Events Table – Follow-up Period (until Day 366)

	Visit Type	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Phone Call**	**Phone Call**	**Clinic Visit**
	Study Day	**85**	**113**	**181**	**209**	**271**	**366**
	Visit Window (Days)	**-7 to +7**	**-7 to +7**	**-7 to +7**	**-14 to +14**	**-14 to +14**	**-14 to +14**
	Visit Number	**7**	**8**	**9**	**10**	**11**	**12**
Study Event	**References**						
Safety							
Assess SAEs	Section 7.1.4	X	X	X	X	X	X

Assess AESI	Section 7.1.4.1	X	X	X	X	X	X
Assess NOCDs, medically attended AEs, AEs leading to withdrawal	Sections 7.1.3	X	X	X	X	X	X
Assess relevant medications	Sections 5.1.2 and 6.5	X	X	X	X	X	X
Blood draws for Immunogenicity and Exploratory Objectives							
Serum Blood Draw (Secondary Objective; 10 mL)	Section 3.5			X			
Whole Blood Draw (Exploratory Objectives; 50 mL)	Section 3.5			X			
Study Completion Procedures							
Study Termination[a]	Section 5.5						X

Notes:
a. Subjects who terminate the study early are recommended to complete certain study-related procedures. See section 5.5 for further details.

LIST OF ABBREVIATIONS

ADCC	Antibody-dependent cell mediated cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BZN	Benzonaphthyridines
CBER	Center for Biologics Evaluation and Research
cDNA	Complementary deoxyribonucleic acid
CI	Confidence interval
CRF	Case report form
CRM_{197}	Cross Reacting Material 197
CSR	Clinical Study Report
DMC	Data Monitoring Committee
EC	Ethics committee
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
ELISPOT	Enzyme-Linked ImmunoSpot
EMA	European Medicines Agency
FACS	Fluorescence-activated cell sorting
FAS	Full analysis set
FDA	Federal Drug Agency
GCP	Good clinical practice
GMC	Geometric mean concentration
GMP	Good manufacturing practice

GMT	Geometric mean titer
GMR	Geometric mean ratio
HEENT	Head, ears, eyes, nose and throat
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
hSBA	Human complement serum bactericidal assay
ICF	Informed consent form
ICH	International Committee for Harmonization
IM	Intramuscular
IRB	Institutional review board
IV	Intravenous
LLQ	Lower limit of quantification
MenC	Meningococcal type C
MPL	Monophosphoryl lipid A
NCR	No carbon required
NOCD	New Onset of Chronic Disease
PEG	Polyethylene glycol
PO	Per oral
PP	Per protocol
RNA	Ribonucleic acid (RNA
SAE	Serious Adverse Event
SMIP	Small molecule immune potentiator
TLR	Toll-like receptor
VSAE	Vaccine serious adverse event

1.0 BACKGROUND AND RATIONALE

1.1 Background

MenC-CRM$_{197}$ Conjugate Vaccine

Meningococcal disease worldwide is predominantly a disease of infants and young children. *N. meningitidis* serogroup B and C remain the most prevalent strains in North America and Europe, (Rosenstein, N. et al., 2001) and together cause more than 95% of reported cases of meningococcal disease in Europe (Connolly, M, et al., 1999). In Europe, *N. meningitidis* serogroup C (MenC) is one of the major serogroups causing invasive disease. Case fatality in Germany has ranged between 6% and 8% between 1999 and 2006, and has remained generally consistent across the different European countries, varying between 6-11%, with the case fatality rate being notably higher for serogroup C disease than for serogroup B (European Centre for Disease Prevention and Control, 2011). Since MenC vaccination was added to Germany's routine schedule for children in 2006, there has been a reported decline in MenC incidence. However, the decline was not as rapid when compared to other European countries (Hellenbrand, W. et al., 2013).

The GSK Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) comprises MenC oligosaccharides conjugated to the protein carrier, CRM$_{197}$, a nontoxic mutant of diphtheria toxin. The vaccine has been shown to be safe and immunogenic and able to prime infants, toddlers and young children for immunological memory (see Meningococcal C-CRM$_{197}$ Conjugate Vaccine Summary of Product Characteristics).

In Germany, the Standing Committee on Vaccination (STIKO) of the Robert Koch Institute recommends a single dose of MenC conjugate vaccine in children over the age of 12 months as part of the routine vaccination campaign (Robert Koch Institute Epidemiologisches Bulletin, August 2013). For specific indications, e.g. in case of postexposure prophylaxis, the recommended schedule for primary immunization of infants between 2 to 12 months of age with a MenC conjugate vaccine is two dosages given with an interval of at least 2 months.

Although the Meningococcal C-CRM$_{197}$ Conjugate Vaccine (Menjugate®) represents an example of how vaccination with a well characterized, purified polysaccharide antigen can yield pivotal public health triumphs, there remains a need for further improvement of the MenC vaccine. A more potent MenC vaccine formulation might yield an increase in the magnitude of the antigen-specific immune response enabling a reduction of the antigen dosage. Furthermore, induction of a more rapid antigen-specific immune response may enable a reduction in the number of doses needed for post-exposure prophylaxis in infants.

Vaccine Adjuvants

Immunization with purified protein or polysaccharide antigens typically results in the induction of a modest antibody response with little or no T cell response when compared to vaccines comprised of whole or killed bacteria or viruses that have inherent immunepotentiating activity. The need to increase the immunogenic response of wellcharacterized and purified antigens that display suboptimal immunogenicity when used alone affirms the essential role for the use of adjuvants. Vaccine adjuvants may significantly reduce the amount of antigen needed (Del Giudice, G, et al., 2013) and may induce a more rapid immune response enabling a reduction in the number of doses in a regimen.

Besides reducing the antigen dosage or number of doses in the vaccine regimen, there is now an increased appreciation of the capacity of adjuvants to increase not just overall antibody titer but also to increase the number of functional antibodies and/or antibodies with higher affinity for vaccine antigens. Many pathogens, such as influenza viruses, HIV, human papilloma virus (HPV) and the malaria parasite, display substantial antigenic drift, subtype and/or strain variations. Therefore, the ability of adjuvants to broaden an immune response profile could be crucial to the success of vaccines against such targets. Previous studies have shown that the broadening effect of adjuvants may be mediated via expansion of B cell diversity, not merely through increased titers (Khurana, et al., 2010, 2011). Clinically, antibody response broadening by adjuvants such as AS04 or oil-inwater emulsions has been demonstrated in HPV vaccines and influenza, respectively (Bissett, SL et al., 2014; Del Giudice, G et al., 2013).

One unmet need is the development of vaccines for effective T cell responses. Several vaccines in development are aimed at eliciting T cell responses, which historically have not been induced by the most commonly used adjuvants in vaccines for human use, such as aluminium hydroxide. Therefore, an objective of many adjuvant discovery and development programs is to elicit more effective engagement of T-helper cells for optimizing the quality, breadth and durability of antibody responses, or, to induce effector CD4+ or CD8+ T cells to kill intracellular pathogens. One approach for new generation vaccines is the use of agonists for Toll-like receptors (TLRs) that activate innate immune receptors, mainly on antigen presenting cells, and facilitate the generation of T helper cell responses.

Adjuvants that are currently employed in human vaccines licensed for use in the USA and/or Europe include aluminium salts, oil-in-water emulsions (MF59, AS03 and AF03), virosomes, and AS04 (Alving, CR, et al., 2012). Among the most advanced adjuvants systems is AS04 which is used in the Cervarix® HPV vaccine and consist of the TLR4

ligand monophosphoryl lipid A (MPL) combined with aluminium salt. MPL, along with QS21, is also part of the adjuvant system (AS01) in the RTS, S malaria vaccine which has been evaluated in a Phase 3 clinical trial (Regules, JA, et al., 2011). Another clinically advanced adjuvant is CpG oligodeoxynucleotide (ODN), a TLR9 ligand contained in the Heplisav® vaccine candidate for hepatitis B from Dynavax, that has completed a Phase 3 clinical trial (Reed, SG, et al., 2013).

Small molecule immune potentiators as a new class of vaccine adjuvants

A new class of adjuvants, small molecule immune potentiators (SMIPs), has been identified that activate immune cells by targeting TLR7 and TLR8. Imiquimod and Resiquimod (R848) are clinically advanced TLR7 and/or TLR8 SMIPs that are used as immunotherapeutics. Although Imiquimod and Resiquimod have been studied extensively as vaccine adjuvants in preclinical models (Vasilakos et al. 2013), they were never optimized for this use and, in general, compare poorly to other pre-clinical and clinical adjuvant candidates. Furthermore, when Imiquimod is applied topically (it is a licensed topical treatment for viral and malignant skin lesions) it induces strong local and systemic inflammatory reactions, and is poorly tolerated (Bauza, et al. 2009; Campanelli, et al. 2005; Meyer, et al. 2008).

Unlike traditional drugs, TLR7 SMIPs activate innate immunity and initiate a cascade of immune responses that can have systemic impact and endure after the compound has been cleared from the organism. For SMIPs as vaccine adjuvants this difference is highlighted further by the fact that 2-3 local IM injections drive antigen-specific B and T cell responses at distal sites and these can provide protection in the form of immunologic memory (Tacken, et al. 2011; Ilyinskii, et al., 2014). Therefore, limiting the systemic exposure of the SMIP adjuvants has been postulated as an approach to both increase vaccine efficacy and minimize side effects associated with systemic and generalized inflammation. GSK is currently developing a novel adjuvant, containing a SMIP from the benzonaphthryridines (BZN) series, LHD153, which targets TLR7. The objective driving the discovery of this new TLR7 ligand was to develop a vaccine adjuvant with high efficacy in increasing the vaccine specific immune response and with minimal side effects. To obtain this objective it was postulated that the ideal compound would remain localized at the site of injection to help trigger the immune reaction to vaccine antigens, yet maintain a low systemic distribution. At the same time this compound had to be soluble to make industrial scale-up and manufacturing feasible. Soluble BZN were engineered so that they could be formulated with aluminium salts with the aim of limiting their systemic exposure and keeping them localized in the muscle for short time after immunization. The strongest adsorption to aluminium hydroxide particles is obtained through ligand exchange of hydroxyl and/or phosphate groups on the surface of aluminium hydroxide or phosphate with soft anionic moieties such as phosphates,

phosphonates, phosphites, sulfates and carboxylates. To drive the adsorption to aluminium hydroxide through ligand exchange, LHD153 was functionalized with a polyethylene glycol (PEG) linker and a terminal phosphonate. Furthermore, LHD153 was stabilized with arginine salt to allow scale up for GMP manufacturing, yielding LHD153R. As predicted, unformulated LHD153R exhibited high levels of systemic exposure when injected IM in mice, rats and dogs, whereas the serum concentrations of LHD153R adsorbed to aluminium hydroxide (Aluminium Hydroxide/LHD153R) was dramatically reduced. Moreover, Aluminium Hydroxide/LHD153R remained localized to the injection site.

Preclinical studies using Aluminium Hydroxide/LHD153R to date confirm the activation of the TLR7 pathway and subsequent boost of both the humoral and cellular immune response. Moreover, Aluminium Hydroxide/LHD153R displays a unique pharmacokinetic profile as demonstrated by its minimal systemic exposure, potentially minimizing any systemic inflammatory response associated with tolerability issues. Aluminium hydroxide/LHD153R has achieved proof of concept in animal models using several vaccine antigens including MenC, MenB, rabies, HIV and respiratory syncytial virus (RSV). In vitro toxicity of LDH153R has been assessed, and in vivo nonclinical tolerability and safety of LHD153R and Aluminium Hydroxide/LHD153R have been evaluated in rats, dogs and non-human primates. LHD153R was not phototoxic, genotoxic or mutagenic (Ames and chromosomal aberration tests), and did not cause local or systemic toxicity in dogs or rats. Furthermore, Aluminium Hydroxide/LHD153R was well tolerated in rhesus monkeys.

1.2 Rationale

The aim of this study is to assess the safety of Aluminium Hydroxide/LHD153R adjuvanted MenC-CRM_{197} conjugate vaccine (MenC-CRM_{197}/Aluminium Hydroxide/LHD153R) and to compare the antibody-mediated immune response elicited by MenC-CRM_{197}/Aluminium Hydroxide/LHD153R with the licensed aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (Menjugate®).

Furthermore, a comprehensive set of exploratory objectives has been selected to assess the systemic exposure of LHD153 after intramuscular injection and to evaluate the quality of the specific immune response against MenC-CRM_{197} in detail and to evaluate biomarkers that may be predictive of safety and/or innate immune activation.

The licensed Meningococcal C-CRM_{197} Conjugate Vaccine (Menjugate®) has been chosen as the primary vaccine candidate to assess the safety and immunopotentiating properties of Aluminium Hydroxide/LHD153R for several reasons. Firstly, the safety and

immunogenicity profiles of the Meningococcal C-CRM$_{197}$ Conjugate Vaccine have been well established through years of commercial use. Secondly, a more potent Meningococcal C-CRM$_{197}$ Conjugate Vaccine might enable a reduction of the antigen dosage or the number of doses needed in infants between 2 and 12 months of age. Finally, Meningococcal C-CRM$_{197}$ is a well-characterized, single conjugate antigen preparation which provides an ideal setting to explore the potential of this new Aluminium Hydroxide/LHD153R adjuvant.

2.0 OBJECTIVES

2.1 Primary Objectives

Primary Safety Objective

To assess the safety of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R as compared to that of aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine.

Primary Immunogenicity Objective

To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine at Day 29, as measured by human complement serum bactericidal assay (hSBA) directed against MenC.

2.2 Secondary Objectives

Secondary Immunogenicity Objective(s)

1. To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal CCRM$_{197}$ Conjugate Vaccine at Day 8 and Day 181 after vaccination, as measured by hSBA directed against MenC. Baseline antibody titers will also be measured by hSBA.
2. To compare the antibody responses of MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal CCRM$_{197}$ Conjugate Vaccine, at Day 8, Day 29 and Day 181 after vaccination, as measured by an enzyme-linked immunosorbent assay (ELISA) to MenC. Baseline antibody concentrations will also be measured by ELISA.

2.3 Exploratory Objectives

1. To evaluate the systemic exposure of LHD153 at several early time-points after IM injection of MenC-CRM_{197}/Aluminium Hydroxide/LHD153R or Meningococcal CCRM_{197} Conjugate Vaccine.
2. To explore the frequency of B cells specific for MenC polysaccharide and CRM_{197} protein at baseline (Day 1) and at Day 8, Day 29 and Day 181 after vaccination with MenC-CRM_{197}/Aluminium Hydroxide/LHD153R or the aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine. Subsequently, the B cell repertoire of the antigen specific B cells will be analyzed in a selected subset of subjects.
3. To explore the baseline T cell mediated immunity to CRM_{197} and to evaluate the frequency and quality of CRM_{197} specific T cells induced by Men$CCRM_{197}$/Aluminium Hydroxide/ LHD153R compared to aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine at Day 8 and Day 29.
4. To evaluate biomarkers that may be predictive for safety and/or innate immune activation.
5. ***To explore the biophysical and functional characteristics of antibodies induced by MenC-CRM197/Aluminium Hydroxide/LHD153R or aluminium hydroxide adjuvanted Meningococcal C-CRM197 Conjugate Vaccine. (Amended: 19 June 2017)***

3.0 STUDY DESIGN

3.1 Overview of Study Design

This is a Phase 1, randomized, observer blind, adjuvant dosage-escalation study. It will be performed at a single center. In total, approximately 80 healthy male and healthy nonpregnant female adults (18-45 years of age) will be enrolled in the study.

Subjects will be randomized to receive a single IM vaccination of either the licensed aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (Menjugate®) or the investigational vaccine, MenC-CRM_{197}/Aluminium Hydroxide/LHD153R.

The dosage of LHD153R will be escalated from 12.5 µg to 100 µg. For the dosageescalation of LHD153R, the subjects will be enrolled into 1 of 4 cohorts, in a stepwise manner with 20 subjects per cohort. Subjects in all cohorts will be randomized in a 1:4 ratio, to receive either aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (control) or MenC-CRM_{197}/Aluminium Hydroxide/LHD153R with increasing doses of LHD153R. Subjects assigned to MenC-CRM_{197}/Aluminium Hydroxide/LHD153R in Cohort 1 will receive 12.5 µg of LHD153R; Subjects in Cohort 2 will receive 25 µg of LHD153R; Subjects in Cohort 3 will receive 50 µg of LHD153R; Subjects in Cohort 4 will receive 100 µg of LHD153R (Table 3.1-1).

Table 3.1-1: Subjects Randomized per Cohort and Treatment Dosage Group

Cohort	Group	Subjects/ Group	MenC Dosage* (µg)	Adjuvant Dosages		Total Volume/Dose	Total Subjects/Cohort
				Aluminium Hydroxide (mg)	LHD153R (µg)		
1	A	4	10	1	0	0.5 mL	20
	B	16	10	1	12.5	0.5 mL	
2	A	4	10	1	0	0.5 mL	20
	C	16	10	1	25	0.5 mL	
3	A	4	10	1	0	0.5 mL	20
	D	16	10	1	50	0.5 mL	
4	A	4	10	1	0	0.5 mL	20
	E	16	10	1	100	0.5 mL	

*Conjugated to 12.5-25 µg CRM_{197}

All cohorts will have a staggered entry. For each cohort, the first 5 subjects (i.e. the first 1:4 randomization block) to receive either aluminium hydroxide adjuvanted

Meningococcal C-CRM$_{197}$ Conjugate Vaccine (n=1) or MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R (n=4) will be vaccinated at rate of 1 subject each day.

After entry of the first 5 subjects in each cohort, the enrollment will be paused. The remaining 15 subjects for each cohort will be enrolled only after DMC review of the safety results obtained through Day 14 has been finalized (Table 3.1-2). In addition, enrollment of the first 5 subjects of the next cohort will only proceed after the Day 14 safety results of the first 5 subjects of the previous cohort have been reviewed by the DMC. Furthermore, all available Day 14 and Day 29 safety results will be included in DMC review between the different enrollment stages.

Table 3.1-2: Overview of staggered entry of subjects based on DMC reviews

Stage	Dosage Cohort	MenC-CRM$_{197}$/ Aluminium Hydroxide (n)	MenC-CRM$_{197}$/ Aluminium Hydroxide /LHD153R (n)
1	1	1	4
Enrollment pause until DMC review of Stage 1 Day 14 Safety Results			
2	1	3	12
	2	1	4
Enrollment pause until DMC review of Stage 1 Day 29 and Stage 2 Day 14 Safety Results			
3	2	3	12
	3	1	4
Enrollment pause until DMC review of Stage 2 Day 29 and Stage 3 Day 14 Safety Results			
4	3	3	12
	4	1	4
Enrollment pause until DMC review of Stage 3 Day 29 and Stage 4 Day 14 Safety Results			
5	4	3	12

Post-vaccination procedures include collection of urine specimens at Day 1, Day 8 and Day 29 for safety assessment and blood specimens at Day 1, Day 8, Day 29 and Day 181 for safety assessment and evaluation of the primary and secondary immunogenicity endpoints. Furthermore, additional blood specimens will be collected for assessment of exploratory endpoints at Day 1, Day 4, Day 8, Day 29 and Day 181 from those subjects that signed an additional informed consent concerning blood collection for exploratory assessment.

3.2 Study Period

Each subject should expect to participate in the study for approximately 12 months, from the time of enrolment through the last study visit.

3.3 Blinding Procedures

This study is designed as an observer-blind study. For each dosage cohort, subjects, investigators, laboratories and the sponsor will be blinded to vaccine assignments.

To maintain the blindness within each cohort, designated nurse(s) or physician(s) will be responsible for administering the study vaccines to the subjects, and will be instructed not to reveal the identity of the study vaccines neither to the subject nor to the investigative site personnel (investigator, study nurse, monitor) involved in the conduct or monitoring of the trial. This (these) designated individual(s) will have no contact with the subjects after the administration of the study vaccine. Furthermore, unblinded monitors are assigned to reconcile actual vaccine treatment.

Study unblinding, at the group level, is planned for an Interim Analysis of the safety and immunogenicity data obtained up to Day 29 after all cohorts are enrolled and for full unblinding at the End of Study.

Except in the case of medical necessity, a subject's treatment should not be unblinded without the approval of the Sponsor. In such instance of medical emergency, every effort should be made to contact the Sponsor prior to unblinding. If unblinding should occur (by either accidental unblinding or emergency unblinding for a serious adverse event) prior to completion of the study, the investigator must promptly contact the Sponsor and document the circumstances on the appropriate forms.

Emergency unblinding

Emergency unblinding should only be undertaken when it is essential for effective treatment of the subject. The investigator will receive a blinded code break envelope for each subject, with the details of drug treatment included. Emergency code break envelopes must be stored in a secure place but be accessible in case of emergency. In an emergency, the envelope can be opened to determine the treatment. The envelope is not to be opened for any reason other than an emergency. When the investigator opens the envelope he/she must note the date, time, and reason for opening it and retain this information with the case report form documentation. The unblinded treatment code should not be recorded in the case report form.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the code break envelope in case of emergency. The investigator must provide

the subject with an emergency card to contact the clinical unit in cases of emergency and will inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable. Subjects may continue the study after unblinding for safety follow-up.

For emergency unblinding, the corresponding Parexel standard operating procedure should be followed:

- Annotate, sign and date the code break envelope.
- Immediately inform Sponsor.
- Complete the Randomization Code Break Form.
- File the Randomization Code Break Form and the annotated envelope with the participant's source documents.
- Provide the Sponsor as soon as feasible, with a copy of the completed Randomization Code Break Form.

3.4 Data Collection

3.4.1 Data Collected from Subjects

The following data will be collected from each subject over the duration of their study participation:

- Demographic Information
- Adverse Events
- Medical History
- Concomitant Medications
- Vital signs

All data collected must only be identified using the Subject ID, as described in section 5.2.3.

3.4.2 Tools Used for Data Collection

Data will be recorded in the Subject Diary and collected on Case Report Forms (CRFs).

Subject Diary

Subject Diaries will be the only source document allowed for solicited local and systemic adverse events (including body temperature measurements), starting after the initial 24

hours post-vaccination observation period at the clinic. The following additional rules apply to documentation of safety information collected in the Subject Diary:

1. No corrections or additions to the Subject Diary will be allowed after it is delivered to the site.
2. Any blank or illegible fields on the Subject Diary must be described as missing in the CRF.
3. Any corrections to the Subject Diary must be performed by the person completing the Subject Diary and should include a single strike through line through the incorrect value or text with a brief explanation for each change, the initials of that person, and date of correction.

Case Report Forms

This study utilizes CRFs to collect study-related data from each subject. A qualified site staff member(s) is required to enter subject data in the CRFs based on the medical information available in each subject's record. The following additional rules apply to documentation of Subject Diary information collected in the CRFs:

1. The site must enter all readable entries in the Subject Diary into the CRF, including those values that may be biologically implausible (e.g. body temperature: 400°C).
2. Any illegible or implausible data should be reviewed with the subject. If an underlying solicited or unsolicited adverse event is described on review with the subject, this should be described in the source document and reported as an unsolicited adverse event in the appropriate CRF (e.g., if the subject above confirms body temperature of 40°C on the day in which body temperature: 400°C was written into his/her Subject Diary, this fever of 40°C should be recorded in the appropriate CRF).
3. Any newly described safety information (including a solicited adverse event) must not be written into the Subject Diary and must be described in the study file as a verbally reported adverse event. Any adverse event reported in this fashion must be described as an unsolicited adverse event and therefore, entered in the appropriate CRF.

Data should be entered into the CRF in a timely fashion following each subject's clinic visit, study procedure, or phone call. Each subject's CRF casebook will be compared with the subject's source records by a GSK-approved study monitor (or designee) over the duration of the study in order to ensure data collection accuracy.

3.5 Collection of Clinical Specimens

The following clinical specimens are required to be collected from each subject in this study:

- Blood
- Urine

Processing of each specimen should be completed by a qualified site member. Testing of clinical specimens will be performed by a GSK or designated laboratory.

Blood Specimens

Before Vaccination

- At the Pre-vaccination Screening Visit (between Day -28 to -3) one sample of approximately 10 ml blood will be drawn from all subjects.
- At Visit 1 (Day 1) - prior to vaccination – two samples of approximately 10 ml blood will be drawn from all subjects.
- At Visit 1 (Day 1) - prior to vaccination - the following blood samples will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays:
  - One sample of approximately 3 ml
  - Two samples of approximately 5 ml
  - One sample of approximately 70 ml

After Vaccination

- At Visit 1 (Day 1) - 1 hour after vaccination - one sample of approximately 3 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 2 hours after vaccination - one sample of approximately 3 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 4 hours after vaccination - one sample of approximately 3 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.

- At Visit 1 (Day 1) - 6 hours after vaccination – two samples of approximately 5 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 8 hours after vaccination - one sample of approximately 3 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.
- At Visit 1 (Day 1) - 24 hours after vaccination - one sample of approximately 10 ml blood will be drawn from all subjects.
- At Visit 1 (Day 1) - 24 hours after vaccination - the following blood samples will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays:
  - One sample of approximately 3 ml
  - Two samples of approximately 5 ml
  - One sample of approximately 20 ml
- At Visit 2 (Day 4) the following blood samples will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays:
  - One sample of approximately 3 ml
  - Two samples of approximately 5 ml
  - One sample of approximately 20 ml
- At Visit 3 (Day 8) two samples of approximately 10 ml blood will be drawn from all subjects.
- At Visit 3 (Day 8) the following blood samples will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays
  - Two samples of approximately 5 ml
  - One sample of approximately 70 ml
- At Visit 6 (Day 29) two samples of approximately 10 ml blood will be drawn from all subjects.
- At Visit 6 (Day 29) one sample of approximately 50 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.

- At Visit 9 (Day 181) one sample of approximately 10 ml blood will be drawn from all subjects.
- At Visit 9 (Day 181) one sample of approximately 50 ml blood will be drawn from subjects that gave additional informed consent for blood collection for exploratory assays.

The blood will be used for screening and safety laboratory assessments, immunological serology assays, pharmacokinetic analysis, cell mediated immunity assays and gene expression and protein production assays. See section 5.1.2, section 5.2.1 and section 7.0 for additional details.

Processing of each blood specimen should be completed in accordance with the study specific Clinical Specimen Laboratory Manual.

The total amount of blood collected over the study period for all subjects will be approximately 90 ml.

For subjects that signed an additional informed consent for blood collection for exploratory assays the total amount of blood collected over the study period will be approximately 441 ml.

Urine Specimens

Urine will be collected at the Pre-vaccination Screening Visit (between Day -28- to -3), at Visit 1 (Day 1; before vaccination and 24 hours after vaccination), at Visit 3 (Day 8) and at Visit 6 (Day 29). Results will be recorded in the source document and CRF.

Urine will be collected from all subjects for safety laboratory assessments and drugs-ofabuse testing. Furthermore, urine will be collected for pregnancy testing in all females.

3.6 Stopping/Pausing Guidelines

Stopping/pausing guidelines are predefined criteria that halt the conduct of a study (either a vaccine group or the entire study). These guidelines are used to ensure the safety of study subjects.

The following criteria, based on FDA guidance and with grading scales adapted from the CBER Guidance for Industry “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive vaccine Clinical Trials”, will be used for this study:

1. The study will be halted (no new enrollments and no further investigational product administered) and a full safety review by the DMC and the IRB/EC will be performed if one of the following occurs.
   a. One subject experiences a serious adverse event (SAE) assessed as possibly or probably related to investigational product or,
   b. There is a subject death assessed as possibly or probably related to the investigational product.
2. The safety data will also be provided to the health authorities and potential restart of the study will require authorization from IRB/EC and health authorities.If one or more subjects experience a Grade 4 AE (see Appendix C, D, E and F for grading scales), vital sign or clinically significant laboratory abnormality that cannot be clearly attributed to another cause, vaccination will be suspended and a full safety review by the DMC and the IRB/EC will be performed. Potential continuation of the study will require authorization from IRB/EC.
3. If six or more subjects experience a Grade 3 AE (see Appendix A, B, C, D, E and F for grading scales), vital sign or clinically significant laboratory abnormality, dosage escalation will be suspended for that vaccine and a full safety review by the DMC and the IRB/EC will be performed. Potential continuation of the study will require authorization from IRB/EC.

The sponsor or the investigator (following consultation with the sponsor) has the right to discontinue the study at any time. If the clinical study is prematurely terminated, the investigator must promptly inform the study subjects and must assure appropriate therapy and follow-up for the subjects. All procedures and requirements pertaining to the archiving of the documents must be followed. All other study materials (such as study vaccines) must be returned to the sponsor or destroyed after sponsor approval.

3.7 Data Monitoring Committee

An independent DMC will be formed to review safety data during scheduled periodic reviews. The DMC may also perform reviews on an ad hoc basis as needed. DMC membership will consist of at least 3 individuals who are external to the site and sponsor, and will include 1 statistician who is independent from the study team. The names of the independent DMC members are mentioned in the DMC charter.

Subjects will be enrolled in a stepwise manner in each of the four vaccine dosage cohorts (Cohort 1: 12.5 µg LHD153R, Cohort 2: 25 µg of LHD153R, Cohort 3: 50 µg of LHD153R and Cohort 4: 100 µg of LHD153R). The DMC will review all safety data, as described in the DMC charter and in the Statistical Analysis Plan, after the first 5 subjects

in each cohort have completed Visit 4 and their data are available for analysis, and before enrollment of the remaining subjects in the respective cohort and before enrollment of the first 5 subjects in the subsequent cohort. In addition, in between the different enrollment stages, the DMC will review all available safety data of subjects that have completed Visit 4 and all available safety data of subjects that have completed Visit 6.

The specific roles and responsibilities of the DMC members and other personnel involved will be documented in the DMC charter. The DMC charter will be finalized before the start of the study and will outline in detail all pausing and stopping rules according to the Clinical Study Protocol.

3.8 Premature Withdrawal from Study

Subjects may withdraw at any time, or be dropped from the study at the discretion of the investigator should any untoward effects occur and/or for safety reasons. In addition, a subject may be withdrawn by the investigator or the Sponsor if he/she violates the study plan or for administrative reasons. The investigator or study coordinator must notify the Sponsor immediately when a subject has been withdrawn due to an adverse event.

The circumstances above are referred to as premature withdrawal from the study, and the reason for premature withdrawal should be clearly documented and detailed in the source documentation. The investigator should make every attempt to evaluate the subject's safety, including resolution of ongoing AEs, at the time of premature withdrawal. If a subject wants to withdraw from the study prior to the last planned study visit, the subject will be asked to be followed for safety for the duration of the study. When a subject withdraws, or is withdrawn, from the study, the procedures described in section 5.5.1 should be completed if possible.

The reasons for premature withdrawal from the study include: Adverse event, death, withdrawal of consent, lost to follow-up, administrative reason, and protocol deviation. These reasons are described in greater detail below.

Adverse Event

For any subject withdrawn from study participation prior to the planned Study Termination Visit, it is important to determine if an AE was associated with the reason for discontinuing the study. This AE must be identified on the appropriate CRF page by indicating "Withdrawn from study due to AE". Any ongoing AEs at the time of study withdrawal must be followed until resolution or stabilization.

Death

For any subject withdrawn from study participation due to death, this should be noted on the appropriate CRF page and the associated SAE that led to the death must be reported.

Withdrawal of consent

The subject can withdraw consent for participation in the study at any time without penalty or loss of benefit to which the subject is otherwise entitled. Reason for early termination should be deemed as "withdrawal of consent" if the subject withdraws from participation due to a non-medical reason (i.e., reason other than AE). If the subject intends to withdraw consent from the study, the investigator should clarify if the subject will withdraw completely from the study or if the subject will continue study participation for safety, or a subset of other study procedures. If the subject requests complete withdrawal from the study, no further study interventions will be performed with the subject.

Lost to Follow-Up

For subjects who fail to show up for study visits (clinic or telephone contacts), study staff is encouraged to make at least three documented attempts to contact the subject by telephone and at least one documented written attempt to contact the subject to encourage the completion of study termination procedures. These efforts to contact the subject must be recorded in the source document. The termination date for the subject to be captured on the appropriate CRF page is the date of the last contact (clinic visit or telephone) with the subject.

Administrative Reason

Examples for subjects withdrawn from the study due to administrative reason can include: Sponsor decision to terminate the study, subject meeting a pre-specified withdrawal criterion, subject discontinuation for insurance issues, moving, no time, etc. This reason should be noted in the appropriate CRF page and any ongoing AEs at the time of study withdrawal must be followed until resolution/stabilization.

If the clinical study is prematurely terminated by the Sponsor, the investigator is to promptly inform the study subjects and local EC/IRB and should assure appropriate therapy and follow up for the subjects. All procedures and requirements pertaining to the archiving of study documents should be followed. All other study materials (study medication/vaccines, etc.) must be returned to the Sponsor.

For subjects who are withdrawn from the study due to receipt of an excluded medication/vaccination or due to significant protocol non-compliance, this reason should be noted in the appropriate CRF page.

Protocol Deviation

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. In general, subjects associated with protocol deviations may remain in the study unless continuation in the study jeopardizes the subject's health, safety, or rights.

Investigators will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact GSK or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a change to the protocol would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by GSK and approved by the IRB/EC and health authorities it cannot be implemented.

Any subject who becomes pregnant during the study should be encouraged to continue participating in the study for safety follow-up. The site must complete a Pregnancy Report CRF (initial report) as soon as possible after learning of pregnancy occurrence (see section 7.1.6 for further details). If the subject withdraws from the study for any of the above categories except death, the site will obtain permission from the subject to continue to remain in contact with her until the outcome of the pregnancy is known, even if the outcome is not known until after the subject reaches the end of the routine study period.

3.9 End of Study

Most clinical trials intended to support the efficacy/immunogenicity and safety of an Investigational Product proceed to full completion of planned sample size accrual.

A subject is considered to have completed this study when he/she has: (1) received the intended dose of study vaccine and (2) completed 365 days (Visit 12) of safety follow-up after receiving the study vaccine.

Evaluation of the primary and secondary immunogenicity objectives requires the testing of biological samples from all study subjects, which can only be completed after all samples are collected. The last samples for the analysis of the primary and/or secondary objectives will be taken at Visit 9 (Day 181). For the purpose of this protocol, End of

Study is defined as the completion of the testing of such biological samples, to be achieved no later than 8 months after collection of the last biological sample at Visit 9.

4.0 SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

In order to participate in this study, all subjects must meet all of the inclusion criteria described.

1. Male or female individuals of 18 through 45 years of age on the day of informed consent.
2. Healthy volunteers with good physical and mental health status, determined on the basis of the medical history, a physical examination and the results of the screening tests as judged by the investigator.
3. Individuals who have voluntarily given written informed consent after the nature of the study has been explained according to local regulatory requirements, prior to study entry.
4. Individuals who can comply with study procedures including follow-up[1].
5. Individuals that are able to understand, read and write German language.
6. Females of childbearing potential who are using an effective birth control method[2] which they intend to use for at least 30 days after the study vaccination.

4.2 Exclusion Criteria

Each subject must not have or must not be:

1. Progressive, unstable or uncontrolled clinical conditions.
2. Hypersensitivity, including allergy, to any component of vaccines, medicinal products or medical equipment whose use is foreseen in this study.

[1] A subject is considered to be compliant if the Investigator judges that the subject will complete the Subject Diary, return for all the follow-up visits and be available for telephone calls as scheduled in the study.

[2] The following birth control methods are considered effective:

- Hormonal contraceptive (such as oral, injection, transdermal patch, implant) if used for at least 30 days prior to informed consent
- Diaphragm with spermicide, tubal occlusion device
- Intrauterine device (IUD)

- Tubal ligation
- Male partner using condom with spermicide
- Male partner having been vasectomized at least six months prior to informed consent

3. Clinical conditions representing a contraindication to intramuscular vaccination and blood draws.
4. Abnormal function of the immune system resulting from:
   a. Clinical conditions.
   b. Systemic administration of corticosteroids (PO/IV/IM) for more than 14 consecutive days within 90 days prior to informed consent.
   c. Administration of antineoplastic and prescription immunomodulating agents or radiotherapy within 90 days prior to informed consent.
5. Received immunoglobulins or any blood products within 180 days prior to informed consent.
6. Received an investigational or non-registered medicinal product within 30 days prior to informed consent or intend to participate in another clinical study at any time during the conduct of this study.
7. Vulnerable subjects (e.g. persons kept in detention), study personnel or an immediate family or household member of study personnel, subjects with legal incapacity or limited legal capacity
8. Any relevant deviation from the laboratory parameters at screening as judged by the investigator.
9. Previously received any vaccine that included a MenC antigen.
10. Previously suspected or confirmed disease caused by *N. meningitides.*
11. Had household contact with and/or intimate exposure to an individual with culture proven MenC.
12. A positive serum or urine pregnancy test prior to the study vaccine administration or are currently lactating.
13. A positive drugs-of-abuse test prior to the study vaccine administration
14. Received any other vaccines within 30 days prior to enrolment in this study or who are planning to receive any vaccine within 30 days from the administration of study vaccines.

15. Any other condition that, in the opinion of the investigator, might interfere with the results of the study or pose additional risk to the subject due to participation in the study.

4.3 Criteria for Delay of Vaccination or Blood Draw

There may be instances when individuals meet all eligibility criteria for vaccination or blood draw yet have a transient clinical circumstance which may warrant delay of vaccination or blood draw. Under such circumstances, a subject may be considered eligible for study enrolment after the appropriate window for delay has passed and inclusion/exclusion criteria have been rechecked, and if the subject is confirmed to be eligible.

Reasons for delay of vaccination include:

- Body temperature elevation ≥38.0°C (measured orally) within 3 days prior to intended study vaccination.
- Use of antipyretics and/or analgesic medications within 24 hours prior to vaccination.

Reasons for delay of blood draw include:

- Subject has received a dose of systemic antibiotics less than 6 days before blood collection for the hSBA directed against MenC.

5.0 STUDY PROCEDURES

The sections that follow provide an overview of the procedures that are to be followed in enrolling, evaluating, and following subjects who participate in this clinical study. Visits can be either clinic visits or safety follow-up telephone calls, as specified in the Table below and in the Time and Events Tables 3 and 4 of the Study Synopsis.

Table 5.0-1: Study procedures

Visit Category	Procedures
Pre-vaccination Clinic Visit	Section 5.1 describes procedures to be followed prior to subject enrollment, including: informed consent and screening procedures.
Vaccination Clinic Visit	Section 5.2 describes procedures to be followed during the vaccination clinic visit, including: prevaccination procedures, enrolment, randomization, vaccination and post-vaccination procedures.
Post-vaccination Visits	Section 5.3 describes follow-up clinic visits and safety follow-up calls.
Unscheduled Visits	Section 5.4 describes possible procedures to be followed at unscheduled clinic visit.
Study Termination Visit	Section 5.5 describes procedures to be followed at the last study visit for a subject (may include early termination visit).

5.1 Pre-vaccination Clinic Visit(s)

The Pre-vaccination Clinic Visit must be performed in the period between Day -28 and Day -3.

This section describes the procedures that must be performed for each potential subject prior to enrollment, including obtaining informed consent and screening.

5.1.1 Informed Consent

"Informed consent" is the voluntary agreement of an individual or his/her legal guardian(s) to participate in research. Consent must be given with free will of choice, and without undue inducement. The individual must have sufficient knowledge and understanding of the nature of the proposed research, the anticipated risks and potential benefits, and the requirements of the research to be able to make an informed decision.

Informed consent following local IRB/EC guidance **must** be obtained before conducting any study-specific procedure (i.e., all of the procedures described in the protocol). Prior to any additional blood sample collection for exploratory objectives, a secondary informed consent **must** be signed by subjects. The process of obtaining informed consent should be documented in the subject source document in addition to maintaining a copy of the signed and dated informed consent.

5.1.2 Screening

After an individual has consented to participate in the study and informed consent is signed, that individual will be given a unique Screening Number. The subject's unique Screening Number will be documented in the Screening and Enrolment log. The eligibility of the subject will be determined based on the inclusion and exclusion criteria listed in section 4.0 and evaluated during this screening procedure.

Screening procedures at the Pre-vaccination Clinical Visit (between Day -28 and Day -3) will include the following:

- Review of demographic data, including age, gender, race, body weight and height.
- Review of medical history, including but not limited to any medical history, ongoing illnesses or injuries that may be relevant to subject eligibility for study participation. Relevant medical history can also include any medical history that contributes to the understanding of an adverse event that occurs during study participation, if it represents an exacerbation of an underlying disease/pre-existing problem.
- Perform physical examination, including but not limited to:
  - Assessment of general appearance
  - Collection of vital signs, including body temperature, blood pressure, heart rate and respiratory rate
  - Examination of head, ears, eyes, nose and throat (HEENT)
  - Examination of skin
  - Auscultation of heart and lungs
- Collection and review of prior and concomitant medications or vaccinations taken prior to start of study (refer to section 6.5 for further details).
- Collection of any unsolicited AEs occurring prior to administration of the study vaccine.

- Blood draw (approximately 10 ml) for Safety Laboratory assessments, measurement of Hepatitis B surface antigen, anti-Hepatitis C virus antibodies, anti-HIV 1 and 2 antibodies and serum pregnancy test (all women).
- Urine sample for Safety Laboratory assessments and drugs-of-abuse testing.

NOTE: A general physical examination is to be performed by a qualified health care practitioner. "Qualified health care practitioner" refers to any licensed health care professional who is permitted by institutional policy to perform physical examinations and who is identified within the Study Staff Signature Log.

Data collected during the Pre-vaccination Screening Clinic Visit must be written in the source document (see section 9.1) and will be captured in the screening CRF Forms. In the event that the individual is determined ineligible for study participation, he/she is considered a screen failure. The reason for screen failure must be documented in the Screening and Enrolment log.

5.2 Vaccination Clinic Visit(s)

This section describes the procedures to be performed at the Vaccination Clinic Visit (Visit 1, Day 1), including: pre-vaccination procedures, enrolment, randomization, prevaccination blood draw, vaccination and post-vaccination procedures.

5.2.1 Pre-vaccination Procedures

During pre-vaccination procedures at Visit 1 (Day 1), the eligibility of the subject will be confirmed based on the inclusion and exclusion criteria listed in section 4.0.

Pre-vaccination procedures at Visit 1 (Day 1) will include the following:

- Review of systems by means of a structured interview that queries the subject as to any complaints the subject has experienced across each organ system.
- Perform physical examination, including but not limited to:
  - Assessment of general appearance
  - Assessment of body weight and collection of vital signs, including body temperature, blood pressure, heart rate, and respiratory rate
  - Examination of head, ears, eyes, nose and throat (HEENT)
  - Examination of skin

- Auscultation of heart and lungs

- Collection and review of prior and concomitant medications or vaccinations taken, or recalled, since the last visit (refer to section 6.5 for further details).
- Collection of any unsolicited AEs occurring prior to administration of the study vaccine.
- One blood sample (approximately 10 ml) will be drawn from all subjects for serology testing.
- One blood sample (approximately 10 ml) will be drawn from all subjects for baseline Safety Laboratory assessments.
- One urine sample for baseline Safety Laboratory assessments, pregnancy testing (all women) and drugs-of-abuse testing.
- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and volume of blood draws are provided in section 3.5.

NOTE: A general physical examination is to be performed by a qualified health care practitioner. “Qualified health care practitioner” refers to any licensed health care professional who is permitted by institutional policy to perform physical examinations and who is identified within the Study Staff Signature Log.

Data collected during pre-vaccination procedures at Visit 1 must be written in the source document (see section 9.1). In the event that the individual is determined ineligible for study participation, he/she is considered a screen failure. The reason for screen failure must be documented in the Screening and Enrolment log. If the individual is determined to be eligible for the study, he/she can be enrolled into the study.

5.2.2 Enrolment

After an individual is determined to be eligible for study participation, the investigator will enroll the subject into an Electronic Data Capture (EDC) system where the randomization to the treatment group will occur. The Screening Number ceases to be used and remains in the Screening and Enrolment Log only.

If for any reason, after signing the informed consent form (ICF), the subject who is eligible and enrolled fails to be randomized, this is called a randomization failure. In this case the early termination study procedures must be applied. The reason for all randomization failures should be recorded in the Screening and Enrolment Log and in the

source document as specified in the Source Data Agreement. The information on subjects who are randomization failures should be kept distinct from subjects who are screen failures, as described in section 5.1.2 and section 5.2.1.

5.2.3 Randomization

Enrolled subjects will be randomized and automatically assigned a unique Subject ID. The Subject ID will be the subject's unique identification number for all CRFs and associated study documentation that will be used for the duration of the study.

If for any reason, after signing the informed consent form (ICF), the eligible subject is enrolled and randomized but fails to undergo treatment, this is an Early Termination and the reason should be recorded in source document as specified in the Source Data Agreement/Source Data Verification Form. The information on these Early Termination subjects should be kept distinct in the source documentation from randomization failures, which are described in section 5.2.2.

5.2.4 Vaccination

After completing the pre-vaccination procedures at Visit 1 (Day 1), administer the vaccine to the subject according to the procedures described in section 6.3. Observe the blinding procedures described in section 3.3.

5.2.5 Post-vaccination Procedures

The following post-vaccination procedures will be performed at Visit 1 (Day 1):

- After vaccination, the subject will be observed for at least 30 minutes for any immediate solicited and unsolicited AEs, body temperature measurement and vital signs at 30 min after vaccination. All safety and body temperature data collected during this time are to be recorded in the subject's source document.
- After vaccination, the subject will be observed for at least 24 hours at the clinic including observation for solicited and unsolicited AEs, body temperature measurements. Body temperature measurements must be performed at 2, 4, 6, 8, 10, 12, 18 and 24 hours after vaccination and additional vital signs at 24h after vaccination. All safety and body temperature data collected during this time are to be recorded in the subject's source.
- One blood sample (approximately 10 ml) will be drawn from all subjects at 24 hours after vaccination for Safety Laboratory assessments.

- One urine sample will be collected from all subjects at 24 hours after vaccination for Safety Laboratory assessments.

- From those subjects that signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn in the first 24 hours after vaccination. Details regarding the number and volume of post-vaccination blood draws are provided in section 3.5.

After the initial 24 hours inpatient observation period, a Subject Diary will be used in this study to document solicited and unsolicited AEs until Day 14. The Subject Diary is the only source for collection of solicited AEs after the initial 24 hours inpatient observation period. Therefore, it is critical that the subject completes the Subject Diary correctly.

The following training regarding completion of the Subject Diary must be provided:

- The subject should be trained on how and when to complete each field of the Subject Diary.
- The subject should be trained on how to self-measure local solicited adverse events and body temperature. The measurement of solicited local adverse events is to be performed using the ruler provided by the site.
- The subject should be instructed how to perform body temperature measurement using the thermometer provided by the site. If the subject feels unusually hot or cold during the day, the subject should check their body temperature. If the subject has fever, the highest body temperature observed that day should be recorded in the Subject Diary.

Subject Diary training should be directed at the individual(s) who will perform the measurements of adverse events and who will enter the information into the Subject Diary. This individual may not be the subject, but if a person other than the subject enters information into the Subject Diary, this person's identity must be documented in the Subject Diary. Any individual that writes in the Subject Diary must receive training on completion of the Diary Card at the time of the visit. This training must be documented in the subject's source record.

The site should schedule the next study activity (clinic visit) with the subject.

The subject will receive a written reminder of the next planned study activity. The subject will be reminded to complete the Subject Diary and to contact the site if there are any questions, and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

5.3 Post-vaccination Visit(s)

5.3.1 Subject Diary Reminder, Safety Follow-up and/or Post-vaccination Blood Draw Clinic Visits

Subject Diary reminder, Safety follow-up and/or post-vaccination blood draw clinic visits will be performed on Day 4 (Visit 2), Day 8 (Visit 3), Day 15 (Visit 4), Day 29 (Visit 6), Day 85 (Visit 7), Day 113 (Visit 8) and Day 181 (Visit 9)

At Day 4 (Visit 2) the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. All unsolicited AEs, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. Any concomitant medications or vaccinations associated with those events must also be recorded on the source documents.
- All subjects will be reminded to complete the Subject Diary and to contact the site if there are any questions, and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit. No changes to the Subject Diary should be done at the clinic visit.
- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and volume of blood draws are provided in section 3.5.
- The site should schedule the next study activity (clinic visit) with the subject and the subject will receive a written reminder of the next planned study activity.

At Day 8 (Visit 3) the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. All unsolicited AEs, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be

recorded on source documents. Any concomitant medications or vaccinations associated with those events must also be recorded on the source documents.

- The subject will be reminded to complete the Subject Diary and to contact the site if there are any questions, and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to hospitalization or an emergency room visit. No changes to the Subject Diary should be done at the clinic visit.
- Blood draw (approximately 10 ml) from all subjects for Safety Laboratory assessments.
- Urine sample from all subjects for Safety Laboratory assessments.
- Blood draw (approximately 10 ml) from all subjects for serology testing.

- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and
- volume of blood draws are provided in section 3.5.

  The site should schedule the next study activity (clinic visit) with the subject and the subject will receive a written reminder of the next planned study activity.

At Day 15 (Visit 4) the following procedures will be performed:

- The Subject Diary will be collected and reviewed. No changes to the Subject Diary should be done at the clinic visit. For details on the Subject Diary see sections 3.4.2, and 5.2.5. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. All unsolicited AEs until Day 14, solicited local and systemic AEs persisting at Day 14, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. All concomitant medications or vaccinations associated with those events must also be recorded on the source documents.
- The site should schedule the next study activity (safety phone call) with the subject.
- The subject will receive a written reminder of the next planned study activity. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

At Day 29 (Visit 6) the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. Any solicited local and systemic AEs continuing beyond Day 14, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. All concomitant medications or vaccinations associated with those events must also be recorded on the source documents.

- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and

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- Blood draw (approximately 10 ml) from all subjects for Safety Laboratory assessments.
- Urine sample from all subjects for Safety Laboratory assessments.
- Blood draw (approximately 10 ml) from all subjects for serology testing.

volume of post-vaccination blood draws are provided in section 3.5.

The site should schedule the next study activity (clinic visit) with the subject.

- The subject will receive a written reminder of the next planned study activity. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

At Day 85 and Day 113 (Visit 7 and Visit 8), the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. Any solicited local and systemic AEs continuing beyond Day 14, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. All concomitant medications or vaccinations associated with those events must also be recorded on the source documents.
- The site should schedule the next study activity (clinic visit) with the subject.
- The subject will receive a written reminder of the next planned study activity. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

At Day 181 (Visit 9), the following procedures will be performed:

- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and

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- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. Any solicited local and systemic AEs continuing beyond Day 14, SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal and NOCD must be recorded on source documents. All concomitant medications or vaccinations associated with those events must also be recorded on the source documents.
- Blood draw (approximately 10 ml) from all subjects for serology testing.

  volume of post-vaccination blood draws are provided in section 3.5.

  The site should schedule the next study activity (safety phone call) with the subject.
- The subject will receive a written reminder of the next planned study activity. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

5.3.2 Safety Follow-up Calls

Safety follow-up calls will be performed on Day 22 (Visit 5), Day 209 (Visit 10) and Day 271 (Visit 11) and include the following procedures:

- Safety follow-up calls are calls made to the subject by a healthcare professional designated on the site log. These calls will follow a script which will facilitate the collection of relevant safety information. The subject will be interviewed according to the script, and information relating to solicited local and systemic AEs persisting beyond Day 14 and unsolicited adverse events including SAEs, AESIs, medically attended AEs, AEs leading to study withdrawal, and/or NOCD and concomitant medications or vaccinations associated with those events. All safety information described by the subject must be written down in a designated location within the source document and not written on the script used for the telephone call.

- From those subjects who signed an additional Informed Consent for exploratory assays, additional blood samples will be drawn. Details regarding the number and

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- The site should schedule the next study activity (clinic visit or study termination visit) with the subject.
- The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

5.4 Unscheduled Visits

An unscheduled visit describes a non-routine study visit triggered by a specific event. These could include anticipated or unanticipated adverse events or interventions.

The following procedures should be carried out for all unscheduled visits:

1. Evaluate the subject's vital signs body temperature, heart rate, and blood pressure and perform a symptom-directed physical examination.
2. Record any observed AEs in the source documents.

3. Record any concomitant medications or vaccinations associated with AEs in the source documents.

5.5 Study Termination Visit

The study termination visit is scheduled on Day 366 (Visit 12). The termination visit is a clinic visit. For visit procedures to be performed for a subject whose planned study participation ends prematurely, please see section 5.5.1.

At the Study Termination clinic visit the following procedures will be performed:

- The subject will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken / received in the time since the last clinic visit.
- The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present.
- Medically attended AEs, SAEs, NOCDs, or AESIs will be recorded on source documents.
- All medications taken or vaccines received will also be recorded on the source documents.
- The site will review with the subject the plan of when information relating to the subject's participation in the study may be available (e.g., study results, treatment assignments). It will also be discussed how information relating to the subject's participation in the study will be shared with the subject's healthcare provider, if the subject chooses to share this information.
- The site will complete the termination CRF page and this will mark the completion of the subject's participation in the study.

5.5.1 Early Termination Visit

The date of termination is the date of the last contact in which the subject's health status was assessed or, in cases where the subject does not agree to any further safety follow-up, it is the date consent is withdrawn. This date should be recorded on the appropriate CRF page.

When a subject is withdrawn from treatment or withdraws from the study, the investigator will notify the Sponsor and, when possible, will perform the procedures listed below.

The reason(s) for the early termination must be included in the subject's source documentation. If the Early Termination Visit is a telephone call, collect as much information as possible. Early Termination Visits include subjects who were randomized but not treated.

At the clinic visit or during the telephone call, the following procedures should be performed, when possible:

- Collection and review of Subject Diary (if not already collected).
- Interview of subject to collect unsolicited adverse events, medically attended AEs, AEs leading to withdrawal, SAEs, AESIs, and NOCD.
- Interview of subject to collect concomitant medications and/or vaccinations.
- Symptom-directed physical assessment, at least including measurement of vital signs (body temperature, respiratory rate, blood pressure, heart rate) and a check of general appearance (in case of clinic early termination visit).
- Draw a blood sample (approximately 10 ml) and a urine sample for Safety Laboratory assessment (in case of clinic early termination visit).
- The site will review with the subject the plan of when information relating to the subject's participation in the study may be available (e.g., study results, treatment assignments). It will also be discussed how information relating to the subject's participation in the study will be shared with the subject's healthcare provider, if the subject chooses to share this information.
- The site will complete the appropriate CRF page and this will mark the completion of the subject's participation in the study.

6.0 TREATMENT OF SUBJECTS

All vaccines associated with this study are to be stored separately from other vaccines and medications in a secure location under appropriate storage conditions with temperature monitoring. **All vaccines associated with this study must be checked for expiration date prior to use. Expired vaccines must not be administered to subjects.**

6.1 Study Vaccine(s)

The term 'study vaccine' refers to those vaccines provided by the Sponsor, which will be evaluated as part of the study objectives. The study vaccines specific to this study are described in Table 6.1-1.

Table 6.1-1: Study Vaccine Composition

Group A (Control) Meningococcal C-CRM$_{197}$ Conjugate Vaccine	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM$_{197}$ protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
Sodium Chloride	3.5 mg
Sterile water for injection, up to	0.5 ml

Group B (12.5µg LHD153R) - MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM$_{197}$ protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide/LHD153R Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
LHD153R	12.5 µg
Sodium Chloride	3.4 mg

Histidine	0.1 mg
Tris	30 µg
Sterile water for injection, up to	0.5 ml
Group C (25 µg LHD153R) - MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM$_{197}$ protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide/LHD153R Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
LHD153R	25 µg
Sodium Chloride	3.4 mg
Histidine	0.2 mg
Tris	61 µg
Sterile water for injection, up to	0.5 ml

Group D (50µg LHD153R) - MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM$_{197}$ protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg

Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide/LHD153R Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
LHD153R	50 µg
Sodium Chloride	3.2 mg
Histidine	0.4 mg
Tris	121 µg
Sterile water for injection, up to	0.5 ml
Group E (100µg LHD153R) - MenC-CRM$_{197}$/Aluminium Hydroxide/LHD153R	
Vaccine Component	**Quantity per 0.5 ml dose**
Vial Containing Vaccine Conjugate	
Meningococcal C oligosaccharide conjugated to	10 µg
CRM$_{197}$ protein isolated and purified from *C diphtheria* CRM c7β197M8	12.5-25 µg
Mannitol	7.3 mg
Sodium dihydrogen phosphate monohydrate	0.092 mg
Aluminum Hydroxide/LHD153R Solvent Components (for 0.5 mL dose)	
Aluminum hydroxide	1.0 mg
LHD153R	100 µg
Sodium Chloride	2.9 mg
Histidine	0.8 mg
Tris	243 µg
Sterile water for injection, up to	0.5 ml

6.2 Non-Study Vaccines

The term 'non-study vaccine' refers to those vaccines which will be intentionally given to study subjects but not formally included in the analysis of study objectives.

No non-study vaccines are planned for this study. Any non-study vaccines administered during the study conduct will be captured in the CRF as concomitant medications and/or vaccinations.

6.3 Vaccine Preparation and Administration

The investigator or designee will be responsible for oversight of the administration of vaccine to subjects enrolled in the study according to the procedures stipulated in this study protocol. All vaccines will be administered only by unblinded personnel who are qualified to perform that function under applicable local laws and regulations for the specific study site.

The vaccine components will be provided in 5 separate kits (i.e. one for the control and one for each of the 4 dosage groups). The vaccine components must be mixed prior to vaccination taking into account the appropriate aseptic procedures. Detailed vaccine preparation and administration instructions, including the maximal administration period, will be provided to investigators prior to study start and must be filed in the Investigator Site File.

PRECAUTIONS TO BE OBSERVED IN ADMINISTERING STUDY VACCINE:

- Prior to vaccination, subjects must be determined to be eligible for study vaccination and it must be clinically appropriate in the judgment of the investigator to vaccinate. Eligibility for vaccination prior to first study vaccine administration is determined by evaluating the entry criteria outlined in protocol sections 4.0.

- Study vaccines must not be administered to individuals with known hypersensitivity to any component of the vaccines.

- Standard immunization practices are to be observed and care should be taken to administer the injection intramuscularly. Before administering vaccine, the vaccination site is to be disinfected with a skin disinfectant (e.g., 70% alcohol). Allow the skin to dry. **DO NOT inject intravascularly**.

- As with all injectable vaccines, trained medical personnel and appropriate medical treatment must be readily available in case of anaphylactic reactions following vaccine administration. For example, epinephrine 1:1000, diphenhydramine, and/or other medications for treating anaphylaxis should be available.

6.4 Vaccine Administration Error or Overdose of Vaccine

Vaccine administration error is defined as receiving a dose of study vaccine that was not reconstituted as instructed or administered by a different route from the intended route of administration. An overdose of study vaccine (whether accidental or intentional) is defined when a dosage higher than the recommended dosage is administered in one dose of study vaccine.

Any vaccine administration error or overdose of study vaccine detailed in this protocol must be reported as an adverse event, and if the vaccine administration error or overdose is associated with a serious adverse event, it must be reported as such within 24 hours to the Sponsor.

6.5 Prior and Concomitant Medications and Vaccines

All medications, vaccines and blood products taken or received by the subject within 180 days prior to the start of the study are to be recorded in the appropriate CRF.

Medications taken for prophylaxis are those intended to prevent the onset of symptoms. Medications taken for treatment are intended to reduce or eliminate the presence of symptoms that are present.

NOTE: Use of antipyretics/analgesics within 24 hours prior to vaccine administration is a reason to delay study vaccination (see section 4.3).

Concomitant medications include all medications (including vaccines) taken by/administered to the subject at and after enrolment and must be documented in the appropriate CRF.

When recording concomitant medications/vaccines, they should be checked against the study entry criteria in section 4.0, to ensure that the subject should be enrolled in the study.

6.6 Vaccine Supply, Labeling, Storage and Tracking

The Sponsor will ensure the following:

- Supply the study vaccines.
- Appropriate labeling of all study vaccines provided that complies with the legal requirements of each country where the study is to be performed.

The investigator must ensure the following:

- Acknowledge receipt of the study vaccines by a designated staff member at the site, including:
  - Confirmation that the vaccines were received in good condition
  - Confirmation to the Sponsor of the temperature range during shipment from the Sponsor to the investigator's designated storage location
  - Confirmation by the Sponsor that the vaccines are authorized for use.
- Proper storage of the study vaccines, including:
  - Storage in a secure, locked, temperature-controlled location.
  - Proper storage according to the instructions specified on the labels.
  - Appropriate record keeping and inventory of the study vaccines, including regular documentation of adequate storage temperature.
- Appropriate use of the study vaccines, including:
  - No use of vaccines prior to receipt of authorization for use from the Sponsor.
  - Use only in accordance with the approved protocol.
  - Proper handling, including confirmation that the vaccine has not expired prior to administration.
  - Appropriate documentation of administration of vaccines to study subjects including:
    - Date, dosage, batch/lot numbers, expiration dates, unique identifying numbers assigned to subjects and study vaccines, and time of vaccine administration. This information will be maintained in an accountability log that will be reviewed by the site monitor.
    - Reconciliation of all vaccines received from the Sponsor. Reconciliation is defined as maintaining records of which and how many vaccines were received, which vaccines were administered to subjects, which vaccines were destroyed at the site, and which vaccines were returned to the Sponsor, as applicable.
- Proper adherence to the local institutional policy with respect to destruction of study vaccines.

- Complete record keeping of vaccine use, wastage, return or destruction, including documentation of:
  - Copy of the site's procedure for destruction of hazardous material.
  - Number of doses destroyed, date of destruction, destruction code (if available), method of destruction, and name of individual performing destruction.

Vaccines that have been stored differently from the manufacturer's indications **must not** be used unless the Sponsor provides written authorization for use. In the event that the use cannot be authorized, the Sponsor will make every effort to replace the vaccine supply. All vaccines used in conjunction with this protocol must be stored separately from normal hospital/practice stocks to prevent unintentional use of study vaccines outside of the clinical study setting.

Monitoring of vaccine accountability will be performed by the study monitor during site visits and at the completion of the study.

At the conclusion of the study, and as appropriate during the course of the study, the investigator must ensure that all unused study vaccines, packaging and supplementary labels are destroyed locally (upon approval from Sponsor) or returned to the Sponsor.

7.0 ASSESSMENTS

7.1 Safety Assessment

The measures of safety used in this study are based on previous study data and based on comparable routine clinical/laboratory procedures. They include a close vigilance for, and stringent reporting of selected local and systemic adverse events routinely monitored in vaccine studies as indicators of reactogenicity.

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

The period of observation for AEs extends from the time the subject signs informed consent until he or she completes the specified safety follow-up period (Day 366) or terminates the study early (whichever comes first). AEs occurring after the informed consent form is signed but prior to receiving study vaccine/product will be documented as an adverse event and recorded within the source documents. However, any AEs occurring prior to receipt of any study vaccine will be analyzed separately from “treatment emergent” AEs (AEs occurring after administration of the first study vaccine).

Adverse events are collected as either solicited or unsolicited adverse events. Solicited events are derived from organized data collection systems, such as Subject Diaries or interview.

7.1.1 Solicited Adverse Events

The term “reactogenicity” refers to solicited signs and symptoms (“solicited adverse events”) occurring in the hours and days following a vaccination, to be collected by the subject after the first 24 hours inpatient observation period at Day 1until Day 14, using a pre-defined Subject Diary.

The following solicited adverse events are included in the Subject Diary. Each adverse event is to be assessed using the scoring system shown in Appendix A (Solicited Local AEs) and Appendix B (Solicited Systemic AE):

Solicited Local Adverse Events

Solicited local AEs include:

- injection site erythema
- injection site induration
- injection site pain
- injection site swelling **Solicited Systemic Adverse Events**

Solicited systemic AEs include:

- body temperature ≥38.0°C (as measured orally)
- loss of appetite
- nausea
- fatigue
- generalized myalgia
- generalized arthralgia
- headache - chills
- vomiting
- diarrhea
- generalized rash
- urticaria

Other Solicited Data

Other solicited data collected per Subject Diary include:

- Use of analgesics/antipyretics recorded as “absent” or “present” and summarized by “for treatment” or “for prophylaxis”
- Body temperature as recorded daily, ideally at same time, by the oral route

The study staff must review the data entered into the Subject Diary as described in sections 3.4.2 and 5.3.1.

NOTE: Any solicited adverse event that meets any of the following criteria must be entered into the subjects' source documents (see section 9.1) and also as an adverse event in the appropriate CRF:

- Solicited local or systemic adverse event that continues beyond Day 14 after vaccination.
- Solicited local or systemic adverse event that leads to a visit to a healthcare provider (medically attended adverse event, see section 7.1.3).
- Solicited local or systemic adverse event leading to the subject withdrawing from the study or the subject being withdrawn from the study by the investigator (adverse event leading to withdrawal, see section 7.1.3).
- Solicited local or systemic adverse event that otherwise meets the definition of a serious adverse event (see section 7.1.4).

7.1.2 Unsolicited Adverse Events

An unsolicited adverse event is an adverse event that was not solicited using a Subject Diary and that was spontaneously communicated by a subject who has signed the informed consent.

7.1.3 Evaluation of Adverse Events

Every effort should be made by the investigator to evaluate safety information reported by a subject for an underlying diagnosis and to capture this diagnosis as the event in the AE page. In other words, the practice of reporting only symptoms (e.g., "cough" or "ear pain") are better reported according to the underlying cause (e.g., "asthma exacerbation" or "otitis media").

The severity of events reported on the appropriate CRF page will be determined by the investigator as:

Mild: transient with no limitation in normal daily activity.
Moderate: some limitation in normal daily activity.
Severe: unable to perform normal daily activity.

The relationship of the study treatment to an AE will be determined by the investigator based on the following definitions:

1. Not Related

The AE is not related to an investigational vaccine if there is evidence that clearly indicates an alternative explanation. If the subject has not received the vaccine, the timing of the exposure to the vaccine and the onset of the AE are not reasonably related in time, or other facts, evidence or arguments exist that reasonably suggest an alternative explanation, then the AE is not related.

2. Possibly Related

The administration of the investigational vaccine and AE are considered reasonably related in time and the AE could be explained by exposure to the investigational vaccine or by other causes.

3. Probably Related

Exposure to the investigational vaccine and AE are reasonably related in time and no alternative explanation has been identified.

The relationship of the study treatment to an unsolicited AE will be determined by the investigator.

Note: solicited AEs will not be evaluated for relationship to study treatment. Grading for severity of solicited local and systemic AEs is described in Appendix A and Appendix B.

Adverse events will also be evaluated by the investigator for the co-existence of any of the other following conditions:

- "Medically attended adverse event": an adverse event that leads to a visit to a healthcare provider.
- "New onset of chronic disease" (NOCD): an adverse event that represents a new diagnosis of a chronic medical condition that was not present or suspected in a subject prior to study enrolment.
- AEs leading to withdrawal: adverse events leading to study or vaccine withdrawal.

All AEs, regardless of severity, will be monitored until resolution or until the investigator assesses them as chronic or stable. All subjects experiencing AEs - whether considered associated with the use of the study vaccine or not - must be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a

satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible.

7.1.4 Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose results in one or more of the following:

- Death.
- Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe.
- Required or prolonged hospitalization.
- Persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions).
- Congenital anomaly/or birth defect.
- An important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

Adverse events which do not fall into these categories are defined as non-serious.

It should be noted that a severe adverse event need not be serious in nature and that a serious adverse event need not, by definition, be severe.

Serious adverse events will be captured both on the Vaccines Serious Adverse Event (VSAE) form as well as on the appropriate CRF page. All SAEs will be evaluated by the investigator for relationship of the event to study vaccine. SAEs that are judged to be possibly or probably related to the study vaccine should be reported to the Sponsor as related/suspected events.

The relationship of the study treatment to an SAE will be determined by the investigator based on the following definitions:

1. Related/suspected

The SAE is judged by the investigator to be possibly or probably related to the study vaccine on the appropriate CRF page (see section 7.1.3).

2. Not Related

The SAE is not related if exposure to the study vaccine has not occurred, **or** the occurrence of the SAE is not reasonably related in time, **or** the SAE is considered unlikely to be related to use of the study vaccine, i.e., there are no facts (evidence) or arguments to suggest a causal relationship.

The relationship of the study vaccine to an SAE will be determined by the investigator.

In addition, SAEs will be evaluated by the Sponsor or designee for "expectedness." An unexpected AE is one that is not listed in the current Summary of Product Characteristics or the Investigator's Brochure or an event that is by nature more specific or more severe than a listed event.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the appropriate CRF. If the onset of an event occurred before the subject entered the study (e.g., any pre-planned hospitalization for conditions like cosmetic treatments or for non-emergency routine visits for a pre-existing condition), the hospitalization would not lead to an AE being classified as serious unless, in the view of the investigator, hospitalization was prolonged as a result of participation in the clinical study or was necessary due to a worsening of the pre-existing condition.

7.1.4.1 Adverse Events of Special Interest

Certain adverse events of special interest (AESIs) are monitored after the administration of immunostimulatory agents. All subjects enrolled in this study will be monitored for AESIs for the entire follow-up period. The AESIs will be defined according to MedDRA preferred terms. The investigator will be provided with a list of AESIs prior to study start. Receipt of this list will be notified and stored, along with the list of AESIs, in the Investigator Site File. During the course of the trial the list of AESIs may change. If this occurs, the investigators will be advised of the change and confirmation of receipt will be documented. The updated list of AESIs and documentation of receipt are also stored in the Investigator Site File. The occurrence of any of these adverse events will be treated as a serious adverse event (SAE), meeting the criterion of a "medically important event."

Subjects will be assessed for diagnosis of an AESI at the following visits:

- Pre-vaccination clinic visit (Day -28 to Day -3)
- Visit 1 (Day 1, pre-vaccination)
- Visit 2 (Day 4)

- Visit 3 (Day 8)
- Visit 4 (Day 15)
- Visit 5 (Day 22; Safety Follow-Up Call)
- Visit 6 (Day 29)
- Visit 7 (Day 85)
- Visit 8 (Day 113)
- Visit 9 (Day 181)
- Visit 10 (Day 209; Safety Follow-Up Call)
- Visit 11 (Day 271; Safety Follow-Up Call)
- Visit 12 (Day 366; Study Termination Visit)

At these visits a qualified health care practitioner listed on the site's responsibilities and delegation logs will conduct a review of organ systems and a targeted physical exam and will evaluate subjects for any new signs or symptoms that could indicate one of the AESIs as specified in the list of AESIs stored in the Investigator Site File. They will also interview the subject about recent medical history and any new diagnosis that could indicate an AESI. Medical records related to any new medical event or diagnosis will be requested, reviewed by the site staff, and recorded in the subject's source documents.

A diagnosis of an AESI will be reported in the same manner and time frame as an SAE using the VSAE form. The investigator must notify GSK within 24 hours. The AESI diagnosis, as well as any medications taken to treat the condition, will be recorded in the subject's source documents and on the appropriate CRF.

7.1.5 Methods for Recording Adverse Events and Serious Adverse Events

All findings regarding Adverse Events must be reported on the appropriate CRF page and on the VSAE form, if applicable, which is part of the Investigator Site File. All findings in subjects experiencing AEs must be reported also in the subject's source document.

All SAEs which occur during the course of the study, whether considered to be associated with the study vaccination or not, must be reported **within 24 hours of the site becoming aware of the event** to GSK or its designee. Specific instructions and contact details for collecting and reporting SAEs to GSK will be provided to the investigator.

All SAEs are also to be documented on the appropriate CRF page. Any medication or other therapeutic measures used to treat the AE will be recorded on the appropriate CRF(s) in addition to the outcome of the AE.

After receipt of the initial report, representatives of GSK or its designee will contact the investigator if it is necessary to obtain further information for assessment of the event.

All SAEs must be reported by the investigator to his/her corresponding EC and applicable regulatory authorities in accordance with institutional policy/regulatory requirements and adequate documentation of this notification must be provided to the Sponsor.

GSK or its designee must also comply with the applicable regulatory requirement(s) related to the reporting of suspected unexpected serious adverse vaccine reactions (also known as SUSARs) to the regulatory authority(ies) and the IRB/EC. If a SUSAR or other safety signal relating to use of one of the study vaccines is reported to GSK or its designee, the Sponsor will communicate the information to the investigator and the investigator will be responsible for submitting this information to the EC and other relevant authorities.

7.1.5.1 Post-Study Events

Any suspected SAE that occurs outside of the protocol-specified follow-up period or after the end of the study but considered to be caused by the study vaccine must be reported to GSK or its designee. These SAEs will be processed by GSK or its designee as during the course of the study, until 3 months after the last scheduled study visit. Instructions and contact details for collecting and reporting these suspected SAEs will be provided to the investigator.

7.1.6 Pregnancies

To ensure subjects' safety, each pregnancy in a subject after study vaccination must be reported to GSK within 72 hours of the site learning of its occurrence. If the subject agrees to submit this information, the pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if intended duration of safety follow-up for the study has ended.

Pregnancy data must be recorded on a Pregnancy Report CRF (initial report) and Pregnancy Follow-Up CRF (outcome report).

Any pregnancy outcome meeting the definition of a SAE (see section 7.1.4) must also be reported on the VSAE Report Form.

7.1.7 Safety Laboratory Measurements

Blood and urine samples will be collected from all subjects at the Pre-vaccination Screening, at Visit 1 (pre-vaccination and 24 hours after vaccination), at Visit 3 and at Visit 6 as outlined in Time and Events Table 3. The blood safety laboratory assessments will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, liver function tests (ALT, AST), a complete blood count and C-reactive protein. The urine safety laboratory assessments will include protein, glucose and red blood cells. An additional blood and urine sample will be collected in case of a clinic Early Termination Visit as outlined in section 5.5.1.

All testing will be conducted by qualified and certified laboratories. The Investigator **must** assess all safety laboratory results. Abnormal laboratory values must be classified by the Investigator as clinically significant or not. Abnormal laboratory values that are considered clinical significant will be defined following the FDA CBER Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" dated September 2007, or the institution's normal ranges if they differ from CBER guidance. Please see Appendix C, D and E for further details on the Toxicity Grading Scales according to CBER.

Retesting may be performed in case of abnormal values per guidance of the investigator.

7.2 Efficacy Assessment

Efficacy measurement will not be performed as part of this study.

7.3 Immunogenicity Assessment

The measures to assess the primary and secondary immunogenicity endpoints for this study are standard, i.e., widely used and generally recognized as reliable, accurate, and relevant (able to describe the quality and extent of the immune response).

The assay's used in this study to assess the primary and immunogenicity endpoints are human serum bactericidal assay (hSBA) and ELISA specific for MenC

The hSBA is a functional measure of the ability of specific antibodies, in conjunction with human complement, to kill MenC indicator strains, and is widely used and generally recognized as the serological correlate of protection. The specific ELISA will be used to

measure the induction of antibodies directed against MenC following vaccination with the study vaccines.

Blood samples (approximately 10 ml) to obtain serum for hSBA and ELISA assays will be collected at Day 1, Day 8, Day 29 and Day 181 (refer to section 3.5 for detailed specimen collection procedures).

Testing will be conducted by a GSK or designated laboratory in a blinded manner towards the treatment group. Laboratory contact details are listed in the Protocol Ancillary Document.

All data will be captured at the laboratory and transferred via Electronic Data Transfer (EDT)

Details on all blood sample handling steps are described in the Clinical Specimen Lab Manual provided to the study site.

7.4 Exploratory Measurements

In those subjects who agree to a separate Informed Consent, additional blood samples will be collected at Day 1, Day 4, Day 8, Day 29 and Day 181 for exploratory measurements. The purpose of these exploratory measurements is to assess the systemic exposure of LHD153, to further delineate vaccine induced antigen specific immune responses and to evaluate biomarkers that may be predictive for safety and/or innate immune activation.

All exploratory measurements will be conducted by a GSK or a designated laboratory. Laboratory contact details are listed in the Protocol Ancillary Document.

Exploratory measurements may be performed after the Clinical Study Report (CSR) has been completed, in which case these data will be submitted as an addendum to the CSR.

Systemic exposure of LHD153

Systemic exposure of LHD153 will be assessed by analyzing LHD153 blood plasma levels at Day 1 (baseline, 1, 2, 4, 8 and 24h after vaccination) and Day 4 using LC/MS/MS. Time-points for assessment of clinical exposure of LHD153 have been selected based on non-clinical data in dogs and rats.

Vaccine-induced antigen-specific immune responses

The frequency of B cells specific for MenC polysaccharide and CRM_{197} will be determined by enzyme-linked immunosorbent spot (ELISPOT) at Day 1, Day 8, Day 29 and Day 181 in order to evaluate the baseline specific B-cell frequency (Day 1), the peak

of plasmablast responses (Day 8), the peak of B cell memory responses (Day 29), and the persistence of memory B cell responses (Day 181).

Subsequently, the diversity of the antigen specific B-cell repertoire will be analyzed in a selected subset of subjects. The selection of the subset will be based on the most pronounced response to the study vaccines when compared to baseline as determined by the primary and secondary immunogenicity assessment.

The diversity of the elicited B-cell receptors will be assessed through sequence analysis of complementary DNA (cDNA) generated from immunoglobulin (Ig) messenger RNA (mRNA). The Ig cDNAs will be analyzed from antigen-specific B cells obtained at Day 1, Day 29 and/or Day 181 and plasmablasts isolated at Day 8. The analysis of the B-cell receptor diversity does not have the intent nor the capability to identify or rule out any genetic modifications in the RNA or DNA that are presumably linked to disease or predisposition to disease.

The frequency of T cells specific for the CRM_{197} protein at baseline (Day 1), at Day 8 and at Day 29 after vaccination with the study vaccines will be determined by FACS analysis using intracellular staining with a panel of cytokines and surface markers to identify cell populations.

To evaluate the biophysical and functional properties of MenC-specific antibodies induced by the study vaccines, biophysical and cell-based assays will be performed on serology samples collected at Day 1 (baseline), Day 29, and Day 181. Antigen specific antibody isotypes, Fc Receptor binding and the antibody glycosylation state will be assessed. Functional ability of the MenC-specific antibodies to fix complement, to promote antibody-dependent cell mediated cytoxicity (ADCC), to induce phagocytosis (ADCP) and to activate FcR+ cells in vitro will be assessed at Day 1 (baseline), Day 29, and Day 181. (Amended: 19 June 2017)

<u>Early Markers for Safety and Innate immune activation</u>

The evaluation of potential biomarkers of safety and innate immune activation will be performed on blood specimens collected at Day 1 (baseline, 6h and 24h after vaccination) and Day 4.

The vaccine-induced production of inflammatory cytokines and chemokines will be monitored on serum samples using a commercially available electrochemoluminescence assay for a panel of pro-inflammatory cytokines and chemokines, including Eotaxin, Eotaxin-3, GM-CSF, IFN-g, IL-1a, IL-1b, IL-10, IL-12 p70, IL-12/IL-23p40, IL-13,

IL15, IL-16, IL-17A, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-8 (HA), IP-10, MCP-1, MCP-4, MDC, MIP-1a, MIP-1b, TARC, TNF-a, TNF-b, VEGF.

The vaccine-induced expression of genes and gene families will be monitored on whole blood samples using of RNA microarrays by existing technologies. The RNA micro array analysis does not have the intent nor the capability to identify or rule out any genetic modifications in the RNA or DNA that are presumably linked to disease or predisposition to disease.

The vaccine-induced changes in myeloid (e.g. monocytes and dendritic cells) and lymphoid (e.g. NK cells, NKT cells) cell numbers and their activation status will be assessed using flow cytometry.

8.0 STATISTICAL CONSIDERATIONS

8.1 Endpoints

8.1.1 Primary Endpoint(s)

8.1.1.1 Primary Safety Endpoint(s)

The measures for assessing safety and tolerability (by vaccine group within each cohort and by LHD153R adjuvant dosage group overall) are as follows:

- The frequency and percentage of subjects with solicited local and systemic AEs through Day 14. Time intervals after vaccination that will be summarized are:30 minutes post-vaccination, Days 1-4 (without 30 minutes), Days 5-8, Days 8-14, Days 1-8 (without 30 minutes) and Days 1-14 (without 30 minutes).
- The frequency and percentage of subjects with any unsolicited AEs from the day of vaccination (Day 1) to Day 14.
- The frequency and percentage of subjects with SAEs, medically attended AEs, AEs leading to study withdrawal, NOCDs, AESIs for the following time periods: day of signed informed consent until study completion (Day 366), day of vaccination (Day 1) to Day 29, and Day 29 to study completion (Day 366).
- The absolute values and changes in hematology, chemistry, and urinalysis parameters (see section 7.1.7).
- The frequency and percentage of subjects with abnormal laboratory parameter values as classified by investigator normal ranges (low, normal, high) and as classified by CBER toxicity grading scales, when available.

8.1.1.2 Primary Efficacy Endpoint(s)

Not applicable.

8.1.1.3 Primary Immunogenicity Endpoint(s)

The primary immunogenicity endpoints are the GMTs measured by hSBA directed against MenC from samples collected on Day 1 (baseline, before vaccination) and Day 29 as well as the GMR of the titers (Day 29 / Day 1).

8.1.2 Secondary Endpoint(s) 8.1.2.1

Secondary Safety Endpoint(s)

Not applicable.

8.1.2.2 Secondary Efficacy Endpoint(s)

Not applicable.

8.1.2.3 Secondary Immunogenicity Endpoint(s)

The secondary immunogenicity endpoints are:

- GMTs and corresponding GMRs measured by hSBA directed against MenC for samples collected at Day 8 and Day181.
- Percentage of subjects with hSBA seroresponse at Days 8, 29, and 181. Seroresponse is defined as a post vaccination hSBA ≥8 for subjects with a baseline hSBA <4 or have an increase of at least 4 times the baseline hSBA level for subjects with prevaccination hSBA ≥4.
- Antibody geometric mean concentrations (GMCs) against MenC measured by ELISA for samples collected on Days 1 (baseline, prior to vaccination), 8, 29, and 181.
- The percentage of subjects with at least a 4-fold increase in antibody concentrations to MenC as measured by ELISA on Day 8, 29, and 181 relative to baseline (Day 1).

8.1.3 Exploratory *Immunogenicity* Endpoint(s)

The exploratory ***immunogenicity*** endpoints are based on results of testing which may not be performed until after the study report has been finalized and will be further refined prior to testing. They include the following:

- Serum concentration of LHD153 at Day 1 baseline (prior to vaccination), Day 1 (1h , 2h, 4h, 8h, and 24h after vaccination), Day 4 by LC-MS/MS.
- Frequency of MenC polysaccharide-specific and CRM_{197}-specific B cells at Day 1 (baseline), Day 8, Day 29, and Day 181 by ELISPOT.
- Diversity of MenC polysaccharide-specific B-cell repertoire at Day 1 (baseline), Day 8, Day 29, and Day 181 by immunoglobulin cDNA sequencing.
- Frequency and quality of T cells specific for CRM_{197} at Day 1 (baseline), Day 8, and Day 29 by flow cytometry analysis using intracellular staining with a wide panel of cytokines and surface markers to identify cell populations.
- Serum concentrations of a panel of 30 chemokines and cytokines at Day 1 baseline (prior to vaccination), Day 1 (6h and 24h after vaccination), Day 4, and Day 8 by multiplex Electro-chemo-luminescence based assay.
- Gene expression profile in whole blood at Day 1 baseline (prior to vaccination), Day 1 (6h and 24h after vaccination), Day 4, and Day 8 by RNA micro array analysis.
- Number and activation status of myeloid and lymphoid cell populations at Day 1 baseline (prior to vaccination), Day 1 (24h after vaccination), Day 4 and Day 8 by flow cytometry.
- ***Antigen-specific antibody isotype, Fc receptor and antibody glycosylation state will be assessed at Day 1 (baseline), Day 8, Day 29, and Day 181 by biochemical and cell-based assays.***
- ***Functionality of MenC-specific antibodies to fix complement, promote antibodydependent cell mediated cytoxicity (ADCC), induce phagocytosis and activate FcR+ cells in vitro will be also assessed at Day 1 (baseline), Day 8, Day 29, and Day 181. (Amended: 19 June 2017)***

8.2 Success Criteria

The study has no formal statistical hypotheses and will not be declared positive or negative according to given rules. The selection of an appropriate LHD153R adjuvant dosage for future studies will be determined by the joint evaluation of the immunogenicity and safety profiles of each dosage group. **8.2.1 Success Criteria for Primary Objective(s)** Not applicable.

8.2.2 Success Criteria for Secondary Objective(s)

Not applicable.

8.3 Analysis Sets

8.3.1 All Enrolled Set

All screened subjects who provide informed consent and provide demographic and/or baseline screening assessments, regardless of the subject's randomization and treatment status in the study and received a Subject ID.

8.3.2 All Exposed Set

All subjects in the enrolled set who receive a study vaccination.

8.3.3 Safety Set

Safety Set (solicited adverse events and other solicited reactions)

All subjects in the Exposed Set who:

- Provide post vaccination reactogenicity data.

Safety Set (unsolicited adverse events)

All subjects in the Exposed Set who:

- Have post-vaccination unsolicited adverse event records.

Safety Set (overall)

All subjects in the Exposed Set who:

- Have either post-vaccination adverse event or reactogenicity records.

Subjects will be analyzed as "treated" (i.e., according to the vaccine a subject received, rather than the vaccine to which the subject may have been randomized).

8.3.4 Full Analysis Set (FAS) Efficacy/Immunogenicity Set

All subjects in the Enrolled Set who:

- Receive a study vaccination AND provide efficacy/immunogenicity data at relevant time points.

FAS sets will be analyzed “as randomized” (i.e., according to the vaccine a subject was designated to receive, which may be different from the vaccine the subject actually received).

8.3.5 Per Protocol (PP) Set Efficacy/Immunogenicity Set

All subjects in the FAS efficacy/immunogenicity set who:

- Are not excluded due to reasons (see section 8.3.8) defined prior to unblinding or analysis.

PPS are subsets of FAS and should always be defined even if the objectives do not require it.

Examples for subjects excluded due to other reasons than protocol deviations are:

- Subjects who withdrew informed consent.
- Premature withdrawal due to an adverse event.

Exclusions need to be considered by objective/time point, i.e., sometimes not all data of a subject but only part of the subject's data will be removed from the PPS analysis.

8.3.6 Other Analysis Sets

All subjects in the Enrolled Set who consent to additional blood draws, receive a study vaccination AND provide exploratory assay data at relevant time points will be included in an exploratory assay subset.

8.3.7 Subgroups

Selected immunogenicity analyses may be provided based on seropositivity status at baseline.

8.3.8 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. A protocol deviation may be a reason to remove data from an analysis set at the time of analysis. Reportable protocol deviations will be defined as exclusionary from the analysis according to protocol objectives and endpoints, which will

be specified in the Statistical Analysis Plan. In some cases exclusion of data may be due to a reason other than a protocol deviation, e.g. early termination.

8.4 Statistical Analysis Plan

This section provides a summary of the statistical methodology to be used. A more detailed description of analysis methods will be provided in a separate Statistical Analysis Plan which may also include additional exploratory analyses not explicitly mentioned in the following sections.

8.4.1 Analysis of Demographic and Baseline Characteristics

Descriptive statistics (number of non-missing observations, mean, standard deviation, median, minimum and maximum) for age, height and weight at enrolment will be calculated overall and by vaccine group and LHD153R adjuvant dosage.

Distributions of subjects by sex and ethnic origin will be summarized overall and by vaccine group and LHD153R adjuvant dosage.

8.4.2 Analysis of Primary Objective(s)

8.4.2.1 Analysis of Primary Safety Objective(s)

Safety of the study vaccines will be assessed in all subjects in terms of the frequency and percentage of reported AEs as well as by changes in clinical laboratory values.

8.4.2.1.1 Analysis of Extent of Exposure

The frequency and percentage of subjects with vaccinations will be summarized by vaccine group and LHD153R adjuvant dosage, by cohort and overall, for the Enrolled Set.

8.4.2.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events

All solicited adverse events will be summarized according to defined severity grading scales. Use of medication to prevent/treat fever will be summarized according to frequencies and percentages reporting “Yes” and “No”.

Frequencies and percentages of subjects experiencing each adverse event will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic adverse event overall and at each time point will also be presented.

Post-vaccination solicited adverse events reported from Day 1 to Day 14 will be summarized for the intervals Day 1-4 (without 30 minutes), Day 5-8, Day 1-8 (without 30 minutes), Day 8-14 and Day 1-14 (without 30 minutes) by maximal severity and by vaccine group and LHD153R adjuvant. The severity of solicited local adverse events, including injection-site erythema, swelling and induration will be summarized according to categories based on linear measurement: 25-50 mm, 51-100 mm, > 100 mm.

Injection site pain and systemic reactions (except fever) occurring up to Day 14 will be summarized according to “mild”, “moderate” or “severe”.

Each solicited local and systemic adverse event will also be further summarized as “none” versus “any”.

Implausible measurements (for further definition see Statistical Analysis Plan) will be left out of the analysis.

Use of antipyretics and analgesics will be summarized by frequency by type of use (prophylactic versus treatment) and percentage of subjects reporting use. The influence of antipyretics and analgesics use on the occurrence of specific adverse events (e.g., fever, pain) will be assessed.

Body temperature will be summarized by 0.5 °C and 1.0 °C increments from 36.0 °C up to ≥40 °C.

8.4.2.1.3 Analysis of Unsolicited Adverse Events

This analysis applies to all adverse events occurring during the study, judged either as probably related, possibly related, or not related to vaccination by the investigator, recorded in the CRF, with a start date on or after the date of first vaccination. AE starting prior to the first vaccination will only be listed. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class.

All reported adverse events, as well as adverse events judged by the investigator as at least possibly related to study vaccine, will be summarized according to system organ class and preferred term within system organ class. These summaries will be presented by vaccination group and LHD153R adjuvant dosage for each cohort and by interval of study observation. When an adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted.

Separate summaries will be produced for the following categories:

- Serious adverse events.
- Adverse events that are possibly or probably related to vaccine.
- Adverse events of special interest.
- New onset of chronic disease.
- Adverse event leading to withdrawal.
- Adverse events leading to a medically attended visit.
- Adverse event by data source.

Data listings of all adverse events will be provided by subject. In addition, adverse events in the categories above will be provided as listed data.

8.4.2.1.4 Analysis of Safety Laboratory Values

The investigator must review all safety laboratory results (see Section 7.1.7). Abnormal laboratory values and clinically significant changes in values from pre-vaccination (Screening Visit) will be assessed, using medical judgment, based on the FDA CBER Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" dated September 2007, or the institution's normal ranges if they differ from CBER guidance. Please see Appendix C, D and E for further details.

The following information will be provided:

- Change in absolute laboratory value from pre-vaccination (Screening Visit) and Day 1 (Visit 1) baseline to Day 1 (24 hours after vaccination), Day 8 (Visit 3) and Day 29 (Visit 6) after vaccination.
- The classification of laboratory values and/or their changes from pre-vaccination according to the CBER toxicity grading scale.
- 3 x 3 shift tables by visit using the categorization of laboratory values according to institutional normal reference ranges (below, within, above).

8.4.2.2 Analysis of Primary Efficacy Objective(s)

Not applicable.

8.4.2.3 Analysis of Primary Immunogenicity Objective(s)

8.4.2.3.1 Statistical Hypotheses

There are no statistical hypotheses associated with the primary immunogenicity objectives. All analyses are descriptive.

8.4.2.3.2 Analysis Sets

The primary immunogenicity analyses will be based on the per-protocol set (PPS) at Day 29. The primary analyses will be repeated using the Full Analysis Set (FAS) as a measure of the sensitivity/robustness of the results (further details are given in section 8.3).

8.4.2.3.3 Statistical Methods

Before any statistical analysis that assumes normally distributed observations, antibody titers will be $\log_{10}$-transformed. Individual titers below the limit of quantitation (LLQ) will be set to half that limit.

Geometric Mean Titers

The logarithmically (base 10) transformed antibody titers will be modeled using an analysis of covariance (ANCOVA) model with a qualitative factor for LHD153R adjuvant dosage (0 [for unadjuvanted MenC], 12.5, 25, 50 or 100 µg) and log (base 10) pre-vaccination titer as a covariate. The adjusted GMT and the two-sided, 95%, confidence intervals (CIs) of the GMT will be calculated based on this model as will the ratio of GMTs and corresponding CIs. The adjusted GMT and two-sided 95% CIs will be constructed by exponentiation (base 10) of the least square means of the logarithmically transformed (base 10) antibody titer. The ratio of GMTs (LHD153R adjuvant dosage minus MenC), and corresponding two-sided 95% CIs, will be constructed by exponentiation (base 10) of the least square differences obtained from this model. The model can be written as:

$$\log_{10}(y_{ik}) = \mu + \alpha_i + \beta x_{ik} + \varepsilon_{ik}$$

where μ represents a common overall mean, α_i represents the adjuvant dose group i effect, β represents the common slope for the log10 pre-vaccination titer, x_{ik} for subject k in adjuvant dose group I, and ε_{ik} represents random error for subject k in adjuvant dose group i.

Geometric Mean Ratios

The logarithmically (base 10) transformed within subject ratio of antibody titers (Day 29 / pre-vaccination) will be modeled using an analysis of variance model with a qualitative factor for LHD153R adjuvant dosage (0 [for non-LHD153R adjuvanted MenC], 12.5, 25, 50 or 100 µg). The adjusted GMR and the two-sided, 95% CIs of the GMR will be calculated based on this model. The model can be written as:

$\log_{10}(y_{ik}) = \mu + \alpha_i + \varepsilon_{ik}$

where μ represents a common overall mean, α_i represents the adjuvant dose group i effect and ε_{ik} represents random error for subject k in adjuvant dose group i.

Handling of missing values

For immunogenicity data, it may be reasonable to consider missing immunogenicity values as missing completely at random (MCAR), i.e., not informative. Therefore, the primary analysis will comprise a complete case analysis only, without introducing any bias. Imputation methods will not be used.

8.4.3 Analysis of Secondary Objective(s) 8.4.3.1

Analysis of Secondary Safety Objective(s) Not

applicable.

8.4.3.2 Analysis of Secondary Efficacy Objective(s)

Not applicable.

8.4.3.3 Analysis of Secondary Immunogenicity Objective(s)

8.4.3.3.1 Statistical Hypotheses

There are no statistical hypotheses associated with the secondary immunogenicity objectives. All analyses are descriptive.

8.4.3.3.2 Analysis Sets

The secondary immunogenicity analyses will be based on the PPS (further details are given in section 8.3) or the appropriate subset of subjects.

8.4.3.3.3 Statistical Methods

The secondary immunogenicity endpoints are:

- GMTs and corresponding GMRs measured by hSBA directed against MenC for samples collected at Day 8 and Day181.
- Percentage of subjects with hSBA seroresponse at Days 8, 29, and 181. seroresponse is defined as a post vaccination hSBA ≥8 for subjects with a baseline hSBA <4 or have an increase of at least 4 times the baseline hSBA level for subjects with prevaccination hSBA ≥4.
- Antibody geometric mean concentrations (GMCs) against MenC measured by ELISA for samples collected on Days 1 (baseline, prior to vaccination), 8, 29, and 181.
- The percentage of subjects with at least a 4-fold increase in antibody concentrations to MenC as measured by ELISA on Day 8, 29, and 181 relative to baseline (Day 1).

The GMTs for samples collected at Day 8 and Day 181 as well as the GMCs for samples collected at Day 1, Day 8, Day 29, and Day 181 will be analyzed using the same approach as for the primary immunogenicity endpoint.

The remaining immunogenicity endpoints are based on subjects meeting criteria for seroconversion or achieving a certain threshold value. These endpoints will be summarized using frequencies and percentages by LHD153R adjuvant dosage (0 [for non-LHD153R adjuvanted MenC], 12.5, 25, 50 or 100 μg). Two-sided 95% ClopperPearson CIs will also be provided for percentages. For analyses of seroconversion, separate summaries may be provided based on seropositivity status at baseline.

8.4.4 Analysis of Exploratory Objectives

Testing and analyses of exploratory endpoints may be performed after the Clinical Study Report (CSR) has been completed, in which case these data will be submitted as an addendum to the CSR.

In general, concentration and titer results will be summarized for each LHD153R adjuvant dosage group using geometric means and associated 2-sided 95% confidence intervals; and, categorical data will be summarized using frequencies and percentages, with corresponding two-sided, 95% confidence intervals.

8.5 Sample Size and Power Considerations of Primary Objectives

Sample size is not driven by statistical assumptions for formal hypothesis testing, but was based on the safety objective for the study. The table below provides the probability for

various combinations of sample size (N) and presumed true frequency of a given event within an individual vaccine group

Frequency of Event	Probability to Observe at Least 1 Subject with a Given Event For Various Choices of N			
	4	**8**	**12**	**16**
0.05	0.1855	0.3366	0.4596	0.5599
0.10	0.3439	0.5695	0.7176	0.8147
0.15	0.4780	0.7275	0.8577	0.9257
0.20	0.5904	0.8322	0.9313	0.9718
0.30	0.8250	0.9423	0.9862	0.9967
0.40	0.8704	0.9832	0.9978	0.9997

The proposed combinations of sample sizes within each cohort are 4 aluminium hydroxide adjuvanted MenC-CRM$_{197}$ and 16 MenC-CRM$_{197}$ plus an assigned-level of LHD153R adsorbed to aluminium hydroxide. If all four cohorts are fully enrolled, there will be 16 subjects receiving aluminium hydroxide adjuvanted MenC-CRM$_{197}$.

With 16 subjects, events which occur at a frequency of 15% or more will be detected with at least 90% probability; and, events which occur at a frequency of 10% or more will be detected with 81% probability. With 4 subjects, events which occur at a frequency of 30% or more will be detected with at least 80% probability. Intermediate values of 8 and 12 are provided to correspond to sample sizes in the MenC-CRM$_{197}$ after cohort 2 and cohort 3 are fully enrolled.

8.6 Interim Analysis

The DMC will be reviewing the accumulating safety data from the study in order to continue enrollment of subjects within a cohort and whether to enroll subjects into the next cohort.

In addition to these periodic reviews, there will be a safety and immunogenicity interim analysis for the selection of an LHD153R adjuvant dosage based on the data collected through Day 29 from subjects enrolled in all cohorts. This analysis will be performed by personnel not involved in study decisions. The results will be unblinded at the group level thereby preserving the blind for individual subjects. No adjustment to the overall alpha

will be performed as the data collected subsequent to this analysis involve secondary and exploratory endpoints.

9.0 SOURCE DOCUMENTATION, STUDY MONITORING AND AUDITING

Study monitoring and auditing will be standardized and performed in accordance with the Sponsor's or delegated contract research organization's (CRO) standard operating procedures and applicable regulatory requirements (e.g., FDA, EMA, and ICH guidelines).

Prior to enrolment of the first study subject, GSK or delegate will train investigators and/or their study staff on the study protocol, all applicable study procedures, documentation practices and all electronic systems. CRFs must be completed for each enrolled subject (see section 8.3.1 for definition of enrolled subject). Documentation of screened but not enrolled subjects must be maintained at the site and made available for review by the site monitor.

9.1 Source Documentation

Prior to the start of the study, the site staff participating in the study conduct will be instructed on what documents will be required for review as source documents. The kinds of documents that will serve as source documents will be agreed between Sponsor or delegate and investigator and designees and specified in the SDA/Source Data Verification Form prior to subject enrolment.

In addition, source documentation **must** include all of the following: subject identification (on each page), eligibility and participation, proper informed consent procedures, dates of visits, adherence to protocol procedures, adequate reporting and follow-up of adverse events, documentation of prior/concomitant medication/vaccines, study vaccine receipt/dispensing/return records, study vaccine administration information, any data collected by a telephone conversation with the subject and date of completion and reason.

The subject must also allow access to the subject's medical records. Each subject must be informed of this prior to the start of the study and consent for access to medical records may be required in accordance with local regulations.

All safety data reported by subjects must be written down in source documents. If there are multiple sources of information (e.g., Subject Diary, verbal report of the subject, telephone contact details, medical chart) supporting the diagnosis of an adverse event, these sources must be identified in the source documents, discrepancies between sources clarified, the ultimate diagnosis must be justified and written in the source documents, and this diagnosis must be captured in the appropriate CRF page. The CRF must also

capture which source(s) of information were used to determine the adverse event (e.g., subject recall, medical chart, Subject Diary).

9.2 Study Monitoring, Auditing and Source Data Verification

Prior to enrolment of the first study subject, GSK or its designee (e.g., a CRO) will develop a Monitoring Plan to specify how centralized and/or on-site monitoring, including clinical specimens reconciliation, will be performed for the study. Study progress will be monitored as frequently as necessary to ensure:

- that the rights and well-being of human subjects are protected,
- the reported study data are accurate, complete, and verifiable from the source documents and
- the conduct of the study is in compliance with the current approved protocol/amendment(s), GCP and applicable regulatory requirements.

Contact details for the team involved in study monitoring will be provided to the investigator. Study data recorded on CRFs will be verified by checking the CRF entries against source documents in order to ensure data completeness and accuracy as required by study protocol.

Additional documents such as the investigator site file, pharmacy records, and informed consent documentation must also be available for review if requested. Arrangements for monitoring visits will be made in advance in accordance with the monitoring plan, except in case of emergency.

The investigator and/or site staff must make source documents of subjects enrolled in this study available for inspection at the time of each monitoring visit and Sponsor audits, when applicable. These documents must also be available for inspection, verification and copying, as required by regulations, by officials of the regulatory health authorities (e.g., FDA, EMA and others) and/or ECs/IRBs. The investigator and study site staff must comply with applicable privacy, data protection and medical confidentiality laws for use and disclosure of information related to the study and enrolled subjects.

10.0 DATA MANAGEMENT

10.1 Data Entry and Management

In this study, all clinical data (including, but not limited to, AE/SAEs, concomitant medications, medical history, and physical assessments), safety data, and immunogenicity data will be entered into an EDC system, which is compliant with Title 21 Part 11 policies

of the Code of Federal Regulations (FDA, 1997). The data system includes password protection and internal quality checks. The EDC system will be designed and validated by the Sponsor prior to activation for data entry by sites. The investigator or designated delegate must review data entered and electronically sign the CRFs to verify their accuracy.

Access to the EDC system for data entry or review will require training and distinct individual access code assignments to those site staff members who will be entering study data and those involved in study oversight who may review study data. Data are collected within the EDC system, to which the Sponsor and site monitors have exclusively "read only" access.

Paper CRFs will be provided for each pregnant subject by the Sponsor. All appropriate pregnant subject data collected will be recorded on this form. One copy must be retained by the investigator, and all other copies (including the original copy) will be returned as directed by the Sponsor. Instructions on how to complete this form will be provided to the investigator.

10.2 Data Clarification

As part of the conduct of the trial, the Sponsor may have questions about the data entered by the site, referred to as queries. The monitors and the Sponsor are the only parties that can generate a query. All corrections and clarifications will be entered into the EDC system and will be identified by the person entering the information, the reason for the change, as well as the time of the changes made. If changes are made to a previously and electronically signed CRF, the investigator must confirm and endorse the changes

10.3 Data Protection

GSK respects the subjects' rights to privacy and will ensure the confidentiality of their medical information in accordance with all applicable laws and regulations.

The Sponsor as Data Controller according to the European Directive on the protection of individuals with regard to the processing of personal data and on the free movement of such data (95/46/EC) confirms herewith compliance to Directive 95/46/EC in all stages of Data Management.

11.0 RECORD RETENTION

Investigators must retain all study records required by GSK and by the applicable regulations in a secure and safe facility. The investigator must consult a GSK representative before disposal of any study records, and must notify the Sponsor of any change in the location, disposition, or custody of the study files. Essential documents must be retained for 15 years. “Essential documents” are defined as documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. These documents should be retained for a longer period, however, if required by the applicable national regulatory or institutional requirements.

These principles of record retention will also be applied to the storage of laboratory samples, provided that the integrity of the stored sample permits testing.

12.0 USE OF INFORMATION AND PUBLICATION

GSK assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov, and in compliance with current regulations.

GSK also assures that key results of this clinical study will be posted in a publicly accessible database within the required time-frame from the End of Study as defined in section 3.9.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

GSK must be notified of any intent to publish data collected from the study and prior approval from GSK must be obtained prior to submission for publication.

13.0 ETHICS

13.1 Regulatory and Ethical Compliance

The study will be conducted in compliance with the protocol, GCP and applicable regulatory requirement(s).

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, European Directive 2001/20/EC, GSK codes on protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki (European Council 2001, US Code of Federal Regulations, ICH 1997).

13.2 Informed Consent Procedures

Eligible subjects may only be included in the study after providing written informed consent or assent, as described in section 5.1.1. Before the start of the study, the investigator will have the informed consent and any other materials that will be provided to the subjects reviewed and approved by the IRB/EC. This review and approval will be documented and stored with other study documents. The investigator or designee must fully inform the subject or legal guardian of all pertinent aspects of the study. A copy of the written informed consent will be given to the subject or the designee. The subject/designee must be allowed ample time to ask about the details of the study and to make a decision as to whether or not to participate in the study. The subject and/or legal guardian(s) **must** sign the consent form indicating their agreement to participate in the study before any study-related procedures are conducted. The informed consent process may be conducted up to 28 days prior to vaccination on Day 1. If the subject is unable to read and write, a witness must be present during the informed consent discussion and at the time of informed consent signature.

Prior to the start of the study, GSK will provide to investigators a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by GSK before submission to the IRB/EC and a copy of the approved version must be provided to GSK after IRB/EC approval.

Women of childbearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements indicated in the protocol for the duration of the study. In case of doubt on

the ability of a subject to adhere to these requirements, that subject should not be allowed in the study

13.3 Responsibilities of the Investigator and IRB/EC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB/EC before study start. Properly constituted IRB/EC is defined in ICH Guideline for Good Clinical Practice E6 (R1), Section 3 (ICH, 1997). A signed and dated statement that the protocol and informed consent have been approved by the IRB/EC must be given to GSK before study initiation. Prior to study start and at any time the protocol is amended during study conduct, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to GSK monitors, auditors, GSK Clinical Quality Assurance representatives, designated agents of GSK, IRBs/ECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform GSK immediately that this request has been made.

The investigator also responsible for the following:

- Maintaining a list of appropriately qualified persons to whom the investigator has delegated significant study-related duties.
- Demonstrating the capability of recruiting the required number of suitable subjects within the recruitment period.
- Demonstrating sufficient time and staffing to properly conduct and complete the study within the agreed study period.
- Ensuring that all persons assisting with the study are adequately informed about the protocol, the investigational product(s), and their study-related duties and functions
- Ensuring that appropriately trained health care professionals are responsible for all study-related medical decisions and for ensuring appropriate medical care of subjects experiencing any adverse event related to the study.
- If permission to do so is given by the subject, ensuring that the subject's primary healthcare provider is informed of the subject's participation in the study.

The investigator should not implement any deviation from, or changes of the protocol without agreement by the Sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or

administrative aspects of the study (e.g., change in monitor(s), change of telephone number(s)). In addition, the investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to study subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

(a) to the IRB/IEC for review and approval/favourable opinion,

(b) to the Sponsor for agreement and, if required,

(c) to the regulatory authority(ies).

13.4 Protocol Amendments

An amendment is a written description of change(s) to or formal clarification of a study protocol which may impact on the conduct of the clinical study, potential benefit of the clinical study, or may affect subject safety, including changes of study objectives, study design, subject population, sample sizes, study procedures, or significant administrative aspects. An administrative change of a study protocol is a minor correction or clarification that has no significant impact on the way the clinical study is to be conducted and no effect on subject safety (e.g., change of telephone number(s), logistical changes). Protocol amendments must be approved by GSK, health authorities where required, and the IRB/EC. In cases when the amendment is required in order to protect the subject safety, the amendment can be implemented prior to IRB/EC approval. Notwithstanding, the need for formal approval of a protocol amendment, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, GSK should be notified of this action, the IRB/EC at the study site, and, if required by local regulations, the relevant health authority should be informed within 10 working days.

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APPENDIX A: GRADING SCALES FOR SOLICITED LOCAL ADVERSE EVENTS*

(Adapted from CBER 2007b)

Adverse event Following Administration of Injectable Product	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Pain	present but does not interfere with activity	interferes with activity	prevents daily activity
Induration / Swelling / Erythema	25 – 50 mm	51 – 100 mm	> 100 mm

*This toxicity grading scale is adapted from CBER 2007 to enable ease of reporting by Subjects in the source documents for 'patient reported' solicited adverse events.. 'Grade 4' is not listed here but will be defined in the Statistical Analysis Plan as necessary.

APPENDIX B: GRADING SCALES FOR SOLICITED SYSTEMIC ADVERSE EVENTS*

(Adapted from CBER 2007b)

Systemic Adverse event		Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Fever	**°C**	38.0 – 38.4	38.5 – 38.9	39.0 – 40
	°F	100.4 – 101.1	101.2 - 102	102.1 - 104
Chills		present but does not interfere with activity	interferes with activity	prevents daily activity
Loss of Appetite		Loss of appetite without decreased oral intake	decreased oral intake without weight loss	decreased oral intake with weight loss
Nausea		Nausea present but not interfering with oral intake	Nausea leading to decreased oral intake	Nausea leading to minimal to no oral intake
Vomiting		1-2 episodes/24 hours	>2 episodes/24 hours	requires outpatient hydratation
Diarrhea		2-3 loose stools /24 hours	4-5 loose stools /24 hours	6 or more watery stools /24 hours or requires outpatient IV hydration
Generalized Myalgia		present but does not interfere with activity	interferes with activity	prevents daily activity
Generalized Arthralgia		present but does not interfere with activity	interferes with activity	prevents daily activity
Headache		present but does not interfere with activity	interferes with activity	prevents daily activity
Fatigue		present but does not interfere with activity	interferes with activity	prevents daily activity
Generalized Rash		localized area of the skin (1 extremity only)	moderate area of the skin (2 or more body regions without whole body involvement)	most of the skin
Urticaria		localized area of the skin (1 extremity only)	moderate area of the skin (2 or more body regions without whole body involvement)	most of the skin

*This toxicity grading scale is adapted from CBER 2007b to enable ease of reporting by Subjects in the source documents for 'patient reported' solicited adverse events. 'Grade 4' is not listed here but will be defined in the statistical analysis plan as necessary

APPENDIX C: TOXICITY SCALES FOR LABORATORY ABNORMALITIES (SERUM CLINICAL CHEMISTRY)

Serum*,**	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)*****
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN

*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

TOXICITY SCALES FOR LABORATORY ABNORMALITIES

**Laboratory values that fall in the normal range may be assigned a category of "Grade 0."

***The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value. "ULN" = the upper limit of the normal range.

APPENDIX D:

(HEMATOLOGY)

Hematology*,**	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000

TOXICITY SCALES FOR LABORATORY ABNORMALITIES

WBC Decrease cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Platelets Decreased cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000

*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

**Laboratory values that fall in the normal range may be assigned a category of "Grade 0."

APPENDIX E:

(URINE)

Urine*,**	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

TOXICITY SCALES FOR LABORATORY ABNORMALITIES

**Laboratory values that fall in the normal range may be assigned a category of "Grade 0."

APPENDIX F: TOXICITY SCALES FOR VITAL SIGNS

Vital Signs*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Tachycardia - beats per minute	101-115	116-130	>130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute**	40-44	35-39	<35	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141-150	151-155	>155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91-95	96-100	>100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) mm Hg	85-89	80-84	<80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute***	21-23	24-27	>27	Intubation

*Subject should be at rest for all vital signs measurements

**Resting heart rate for young healthy subject population is between 45-90 per minute

***Respiratory rate for young healthy subject population is between 12-20 breaths per minute

APPENDIX G: PROTOCOL AMENDMENTS SUMMARY OF CHANGES

GlaxoSmithKline Biologicals SA

Vaccines R &D

Protocol Amendment 6

eTrack study number	205496 (MENCLHD153R-AL (V132)-001 **and**
Abbreviated Title	(V132_01EXP))
EudraCT number	2014-002430-31

Amendment number:	Amendment 6
Amendment date:	19 June 2017
Co-ordinating author:	PPD Scientific Writer
Rationale/background for changes:	include an adc onality of specific antibodies induced by biophysical the study vaccines.

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

Synopsis

In the **Exploratory Objectives** section, the following objective has been added:

To explore the biophysical and functional characteristics of antibodies induced by MenC-CRM197/Aluminium Hydroxide/LHD153R or aluminium hydroxide adjuvanted Meningococcal C-CRM197 Conjugate Vaccine.

In the **Exploratory endpoints** section, the following text has been added:

Exploratory *immunogenicity* endpoints*:*

Testing and analyses of exploratory ***immunogenicity*** endpoints may be performed after the Clinical Study Report (CSR) has been completed, in which case these data will be submitted as an addendum to the CSR.

- ***Antigen specific antibody isotype, Fc receptor binding capability and antibody glycosylation state will be assessed at Day 1 (baseline), Day 29, and Day 181.***
- ***Functionality of MenC-specific antibodies to fix complement, promote antibodydependent cell mediated cytoxicity (ADCC), induce phagocytosis (ADCP) and activate FcR+ cells in vitro will be also assessed at Day 1 (baseline), Day 29, and Day 181***

Section 2.3: Exploratory objectives: The following objective has been added:

To explore the biophysical and functional characteristics of antibodies induced by MenC-CRM197/Aluminium Hydroxide/LHD153R or aluminium hydroxide adjuvanted Meningococcal C-CRM197 Conjugate Vaccine.

Section 7.4 Exploratory measurements: The following text has been added.

To evaluate the biophysical and functional properties of MenC-specific antibodies induced by the study vaccines, biophysical and cell-based assays will be performed on serology samples collected at Day 1 (baseline), Day 29, and Day 181. Antigen specific antibody isotypes, Fc Receptor binding and the antibody glycosylation state will be assessed. Functional ability of the MenC-specific antibodies to fix complement, to promote antibody-dependent cell mediated cytoxicity (ADCC), to induce phagocytosis (ADCP) and to activate FcR+ cells in vitro will be assessed at Day 1 (baseline), Day 29, and Day 181.

Section 8.1.3 Exploratory *Immunogenicity* endpoint(s): The following text has been added:

The exploratory ***immunogenicity*** endpoints are based on results of testing which may not be performed until after the study report has been finalized and will be further refined prior to testing

- ***Antigen-specific antibody isotype, Fc receptor and antibody glycosylation state will be assessed at Day 1 (baseline), Day 8, Day 29, and Day 181 by biochemical and cell-based assays.***
- ***Functionality of MenC-specific antibodies to fix complement, promote antibodydependent cell mediated cytoxicity (ADCC), induce phagocytosis and activate FcR+ cells in vitro will be also assessed at Day 1 (baseline), Day 29, and Day 181.***

Protocol Sponsor Signatory Approval

eTrack study number and Abbreviated Title	205496 (MENCLHD153R-AL (V132)-001 (V132_01EXP))
Date of protocol Amendment	19 June 2017
Detailed Title	A Phase 1, Randomized, Observer-Blind, DosageEscalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal CCRM197 Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM197 Conjugate Vaccine in Healthy Adults (18-45 years of age)
Sponsor signatory	Antonio Gonzalez Lopez Clinical Research and Development Lead
Signature	_____
Date	_____

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Protocol Investigator Approval

eTrack study number and Abbreviated Title	205496 (MENCLHD153R-AL (V132)-001 (V132_01EXP))
Date of protocol Amendment	19 June 2017
Detailed Title	A Phase 1, Randomized, Observer-Blind, DosageEscalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal CCRM197 Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM197 Conjugate Vaccine in Healthy Adults (18-45 years of age)
Investigator name	
Signature	_____
Date	_____

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Protocol Sponsor Signatory Approval

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Sponsor signatory	Antonio Gonzalez Lopez Clinical Research and Development Lead
Signature	[redacted]
Date	30-JUN-2017

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