CLINICAL STUDY PROTOCOL VS9 77 **Version 1**

A Phase 3b, Controlled, Open-Label, Multi-Center Study to Evaluate Safety and Inumnogenicity of a Single Dose of GlaxoSmithKline's Meningococcal ACWY Conjugate Vaccine (Menveo), Administered to Healthy Individuals 15 through *55* years of age, approximately 4-6 years after primary ACWY vaccination.

Safety and Immunogenicity Study of a Single Dose of Menveo, Administered to Subjects 15 through *55* years of age, approximately 4-6 years after primary ACWY vaccination

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PROTOCOL SYNOPSIS V59 77

Name of Sponsor:	**Protocol number:**	**Gene1i c name of study vaccine(s):**
GlaxoSmithKline Biologicals S.A	V59 77	Meningococcal (groups **A,** C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine

Titl e of Study: A Phase 3b, Controlled, Open-Label,Multi-Center Study to Evaluate Safety and Immunogenicity of a Single Dose of GlaxoSmithKline's Meningococcal ACWY Conjugate Vaccine (Menveo,)Administered to Healthy Individuals 15 througll *55* years of age, approximately 4-6 years after primary ACWY vaccination.

Study **Pe1iod :** Approximately 180 days (six months).	**Clinical Phase:** 3b

Background and Rationale:

Neisseria meningitidis is a leading cause of bacterial meningitis and sepsis worldwide, capable of causing outbreaks and epidemics of invasive disease. Meningococcal disease is associated with higll morbidity and mortality even among patients who receive early antibiotictreatment. Most cases of invasive disease worldwide are caused by serogroups A, B, C, W and Y.

The quadrivalent meningococcal oligosaccharide diphtheria CRM-197 conjugate vaccine (MenACWY-CRM; Menveo, GSK Vaccines) is approved for active inlmunization ofindividuals from 2 months througll *55* years of age in the United States, and in over 60 other countries. As of February 2015, more than 30,000of subjects have been exposed to MenACWY-CRM vaccine in completed clinical studies and more than 24 million doses of the vaccine have been distributed globally.

The US Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination with a quadrivalent conjugated meningococcal vaccine for adolescents at 11-12 years of age with a booster dose administered *5* years later. While a substantial body of data exists showing a robust inlmune response and good antibody persistence after a single dose ofMenACWY-CRM in adolescents, the response to a booster dose of MenACWY-CRM in this agegroup has only been evaluated in 2 clinical studies with limited number of subjects.

A robust anamnestic inlmune response to a booster dose ofMenveo vaccine administered at approximately *5* years after previous vaccination with the same vaccine or a licensed meningococcal oolysaccharide vaccine (Menomune®) was demonstrated in

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the phase 2 clinical study V59P6El . High titers of bactericidal antibodies against the vaccine serogroups were achieved at 7 and 30 days after booster dose in MenACWY-primed subjects. However, the number of subjects included in this studywas relatively small (N=l 0l , including 50 subjects who received a booster dose after the primary MenACWY-CRM vaccination).

In the phase 3b clinical study V59Pl3 El , a booster dose of MenACWY-CRM was given 3 years after primary vaccination with either MenACWY-CRM or Menactra®(a meningococcal diphtheria toxoid-conjugated MenACWY vaccine, MenACWY-D) in adolescents. A booster dose was able to substantially increase antibody titers against all 4 serogroups irrespective of the priming vaccine. Again, only a small number of subjects (N=160) received the MenACWY-CRM booster, (83 who received primary MenACWY-CRM and 77 who received MenACWY-D).

In the light of thecurrent ACIP recommendation for a booster dose of MenACWY-CRM, there exists a need to evaluate the response to a MenACWY-CRM booster given at -5 years after primary vaccination in meningococcaŀvaccine primed adolescents. Generation of this data would also be of relevance in outbreak management and vaccination of travelers to endemic areas.

The purpose/aim of this study is to assess the safety and antibody response to vaccination with a booster dose of Menveo given 4-6 years after primary vaccination and the response to a single dose given to vaccine-naivesubjects, and to describe the immune response over time after a booster dose of Menveo, administered to subjects previously vaccinated with Menveo or Menactra, and after a single dose ofMenveo to vaccine-naive subjects. The inclusion of vaccine-naive subjects in a separate study arm is to enable comparison of the rapidity and magnitude of an anamnestic response to a booster dose (in primed individuals) or the primary response to a first dose (in naive individuals) of MenACWY-CRM.

Study Objectives:

P1i ma ry Objective(s): Immunogenicity objective:

1. To demonstrate a sufficient immune response following a booster dose of MenACWY-CRM (Menveo) vaccine, !riven to subjects who oreviously

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received Menveo, as measured bythe percentage of subjects with hSBA seroresponsel against N. meningitidis serogroups A, C, Wand Y at Day 29 after vaccination

2. To demonstrate a sufficientimmune response following a booster dose of MenACWY-CRM (Menveo) vaccine, given to subjects who previously received Menactra, as measured by the percentage of subjects with hSBA seroresponsel against **N .** meningitidis serogroups A, C, Wand Y at Day 29 after vaccination

Criteria to demonstrate immune response sufficiency The immune response sufficiency will be tested sequentially; first in the group of subjects who received primary vaccination with Menveo and, if met, also in the group of subjects who received primary vaccination with Menactra . The immune response will be considered as sufficient if the lower limit of the one-sided 97.5% CI for percentage of subjects with hSBA seroresponse[1] against serogroups A, C, Wand Y is greater than 75%. The study will be considered successful if the immune response sufficiency will be demonstrated at least in the group of subjects who received primary vaccination with Menveo.

Secondar y Objective(s):

Immunogenicity objectives:

1. To compare the immune responses over time followinga booster dose of MenACWY-CRM vaccine, between subjects who previously received Menveo, subjects who previously received Menactra, and subjects who previously received Menveo or Menactra (pooled vaccine group) and following a single dose in vaccine-naive individuals, as measured by the percentages of subjects with hSBA seroresponse[1] hSBA titers ,::8 and 2:16, and hSBA GMTs against *N. menin<ritidis* seroornuos A. C Wand Y at Dav1. Dav 4 Dav 6 and Dav 29

[1] Seroresponse is defined forthisstudy asfollows: For subjectswith pre-vaccinationtiters <4, pos-t vaccinationtiters2:16; forsubjectswithpre-vaccinationtiters2::4, postvaccinationtitersat least4timesthe pre-vaccinationtiters.

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after vaccination

2. To assess persistence of bactericidal antibodies against serogroups A, C, W and Y at approximately 4-6 years after the primary vaccination with Menveo and after the primary vaccination with Menactra in comparison with naturally-acquired levels in vaccine-naive individuals, as measured by the percentages of subjects with hSBA titers 8 and hSBA GMTs at Day 1.

Safety objectives:

1. To assess reactogenicity and safety of MenACWY-CRM vaccine when administered to subjects who previously received Menveo or Menactra and vaccine-naive individuals.

Study Design:

This is a phase 3b, controlled, open-label, multi-center study to evaluate safety and inlmunogenicity of MenACWY-CRM after a single vaccination in healthy individuals who were vaccinated with Menveo or Menactra 4 to 6 years before and in vaccine-naive individuals.

Study population Approximately 700 healthy subjects 15 through 55 years of age will be enrolled in the study.

Duration of the study The duration of this study is approximately 6 months per subject.

Written informed consent and, as applicable according to local guidelines, written assent will be obtained before conducting any study-specific procedures.

Vaccination schedule: All subjects will receive a single dose of MenACWY-CRM at Day 1.

Study groups:

- Group Menveo-Menveo: approximately 300 subjects, who were vaccinated with a single dose of Menveo 4 to 6 years before, will receive one dose of MenACWY-CRM.
- Grouo Menactra-Menveo: aooroximatelv 300 subiects, who were vaccinated with a

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single dose ofMenactra 4 to 6 years before, will receive one dose ofMenACWY-**CRM.**

- Group Naive: approximately 100 subjects, of similar age to subjects enrolled in other primed groups, with enrolment distributed across all clinical sites, who have not received any meningococcal vaccination, will receive one dose ofMenACWY-**CRM.**

Randomization / Stratification:

Within eachstudy group, subjects will be randomized into one of two different blood draw schedules according to a 1:1 ratio, described as follows:

- Subjects getting blood draws at Day 1, Day4 andDay29.
- Subjects getting blood draws at Day 1, Day 6 and Day 29.

For a schematic overview, see Table 1.

Table I: Schema tic diagra m of the VS9_77 stu dy gro ups

Vacc.ine History	Vacc.ination in current study	Blood drawschedule
Menveo N=300	Menveo	Blood draw Day I, 4, 29 (N=l50)
		Blood draw Day I, 6, 29 (N=150)
Menactra N=300	Menveo	Blood draw Day I, 4, 29 (N=l50)
		Blood draw Day I, 6, 29 (N=l50)
Vaccine-Naive N=l OO	Menveo	Blooddraw Day I, 4, 29(N=50)
		Blooddraw Day I, 6, 29(N=50)

Blinding open-label study.

Blood samn!P.s: Three (3) blood samples of approximately 10 mL each will be collected according to the blood draw schedule in Table 1.

Data collection: Electronic Case Report Form (eCRF).

Studv clinic visits: Three (3) clinic visits at Day 1, Day 4 or Day 6 and Day 29 are

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planned for each subject.

Reminder Phone calls: Two (2) reminder phone calls will be conducted at Day 3 and Day 5 after the study vaccination to remind the subject/ legal guardian to complete the diary card.

Safety phone calls: Three (3) safety phone calls (at Day 15, Day91 and Day181) will be conducted to collect any medically-attended AEs, AEs leading to withdrawal, SAEs, related medications and any vaccinations. In addition, all unsolicited AEs and related medications occurring after the vaccination will be collected during the safety call at Day15. The Day 181 Safety Phone call will also serve as the termination visit.

Solicited Adverse Events (injection site pain, erythema, induration, fatigue, headache, myalgia, arthralgia, loss of appetite, nausea, chills and fever) occurring on the day of vaccination and the following six days (Day I through Day 7) will be recorded daily using a Diary Card for all subjects.

Unsolicited AEs occurring within 28 days after study vaccination will be collected. Qualified site staff will interview the subject by phone approximately 14 days after vaccination and in person at the study site approximately 28 days after study vaccination to assess the occurrence of any unsolicited AEs.

Medically-attended AEs, AEs leading to study withdrawal and SAEs will be collected during the entire study period. These data will be captured by interviewing the subject and/or subjects' parents / guardian (as applicable) during the site visits and phone calls and by review of available medical records. Subjects and/or parents / guardian will be encouraged to call the site in the event of any medically-attended AEs or any AEs which they perceive as being of concern during the entire study period.

Table 2: **Schematic diagram of the VS9_77 study design.**

Day l	Day 4	Day 6	Day15	Day 29	Day 91	Day181
Blood draw (all subjects) Menveo	Blood draw (50% of subj ects)	Blood draw (50% of subjects)	Safety Phone call	Blood draw (all subjects)	Safety Phone call	Safety Phone call Study tennination

Number of Subjects planned: Aooroximatelv 700 subiects are planned for enrolment

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into this study, approximately 300 subjects who previously received Menveo (Menveo-Menveo group), 300 subjects who previously received Menactra (Menactra-Menveo group) and 100 meningococcal vaccine-naive subjects (Naive group). Assuming a 10% drop-out rate that should provide approximately 630 evaluable subjects.

Study Population and Subject Characte1i stics: The list of inclusion and exclusion criteria is included in protocol section 4, Selection of Study Population.

Study Procedures: The study includes three clinic visits, one vaccination, three blood draws, and three safety phone calls for each subject. All study procedures associated with the pre-vaccination, vaccination, post-vaccination and study termination visit are described in section 5.0.

Study Vaccines:

GlaxoSmithKline Meningococcal MenAC\1VY- CRl "\1 vacc in e (M en veo): Meningococcal (groups A, C, W and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine is supplied as a vial that contains 10 µg of serogroup A oligosaccharides and 5 µg of serogroups C, W and Y oligosaccharides, conjugated to *Corynebacterium diphtheri.ae* CRM191 protein. Overall injection volume of 0.5 mL.

The vaccine will be administered intramuscularly, preferably in the deltoid area of the non-dominant arm.

P1i mary Endpoint(s):

Immunogenicity Endpoints:

The following measures will be summarized for Menveo-Menveo and Menactra-

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Menveo groups:

1. Percentage of subjects with hSBA seroresponse[1] against *N. meningitidis* serogroups A, C, W and Y at Day 29.

Secondary Endpoints:

Immunogenicity endpoints:

The following measures will be summarized for Menveo-Menveo, Menactra-Menveo, Naive and the pooled (Menveo-Menveo and Menactra-Menveo) groups:

1. Percentage of subjects with hSBA titer 2:8 and 2:16 against *N. meningitidis* serogroups A, C, W and Y at Day 1, Day 4, Day 6 and Day 29 and between-group differences;
2. Percentages of subjects with hSBA seroresponse[2] against *N. meningitidis* serogroups A, C, W and Y at Day4, Day 6 and Day 29 and between-group differences;
3. hSBA GMTs against *N. meningitidis* serogroup A, C, W and Y at Day 1, Day 4, Day 6 and Day29;
4. Ratios of hSBA GMTs at Day 1, Day 4, Day 6 and Day 29 (between study groups).
5. hSBA Geometric Mean Ratios (G:MRs) at Day 4, Day 6, and Day 29 compared to Day 1 (within study groups).

Safety endpoi nts:

Safety of the study vaccine will be assessed in the Menveo-Menveo and Menactra-Menveo groups and the pooled vaccine group (Menveo-Menveo and Menactra - Menveo) and the vaccine-naive orouo in terms of the fr'"mencies (oercenta2es) of

[1-2] Seroresponse is defined forthisstudy as follows: Forsubjects with prevaccinationtiters<4, post-vaccination titers 2: 16; forsubjects ,vitbprevaccinationtiters 2:4, post vaccination titers4 timestbe pre-vaccination titers.

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reported adverse events including

1. Any unsolicited AEs reported within 30minutes after vaccination;
2. Solicited local and systemic AEs reported from Day 1 (6 hours) through Day 7 after vaccination;
3. Other indicators of reactogenicity(e.g. use of analgesics/ antipyretics, body temperature) within 7 days after vaccination;
4. All unsolicited AEsreported from Day 1 through Day 29 after vaccination;
5. Medically-attended AEs, AEs leading to withdrawal and SAEs reported from Day1 through Day 181 (during the entire study period).

Statistical Analyses:

P1i mary Immunogenicity Objective

The primary population for the analysis of sufficient immune response is the Per Protocol Set (PPS), and will consist of the Menveo-Menveo group (n=270 evaluable subjects) and Menactra-Menveo group (n=270 evaluable subjects). To demonstrate immune response sufficiency after MenACWY-CRM booster vaccine administration, the lower limit of the one-sided 97.5% Confidence Interval (CI) for percentage of subjects with hSBA seroresponse against eacli of serogroups A, C, W and Y must be greater than 75%. This will be tested sequentially first in the group of subjects who received primary vaccination with Menveo and, if met, also in the group of subjects who received primary vaccination with Menactra.

Hypothesis:

Null hypothesis	Alternative hypothesis
p_{ij} 0.75	$p_{ij} > 0.75$

Where: P_{ij} is the population booster seroresponse rate; j = 1,2 refer to group Menveo-Menveo (first test) and Menactra-Menveo (second test) respectively; i = 1,2,3,4 refer to serogroup A, C, W and Y respectively.

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Sample Size:

Statistical power was estimated based on observed data from study V59P13El.

Assuming the true booster seroresponse rates in the Menveo-Menveo group range from 90% to 97% (alternative hypothesis) for each serotype, a sample size of n=270 will have at least 96% power to show sufficiency of immune response to a booster dose of MenACWY-CRM, compared with a pre-specified reference booster seroresponse of 75% (null hypothesis) using an exact test with 0.025 one-sided significance level.

Assuming the true booster seroresponse rates in the Menactra-Menveo group range from 91% to 100% (alternative hypothesis) for eachserotype, a sample size of n=270 will have at least 96% power to show sufficiency of inlmune response to a booster dose of MenACWY-CRM, compared with a pre-specified reference booster seroresponse of 75% (null hypothesis) using an exact test with 0.025 one-sided significance level.

Overall statistical power to show sufficiency of inlmune response to a booster dose of MenACWY-CRM for each serotype in both the Menveo-Menveo and the Menactra-Menveo group will be at least 92%.

When taking a 10% dropout rate into account, N=300 previously vaccinated subjects with Menveo and N=300 previously vaccinated subjects with Menactra have to be enrolled in the study.

Calculations have been done with nQuery Advisor (Version 7.0).

In terim Analysis: No interim analysis is planned for this study.

Data Monito1i ng Committ ee: No DMC will be utilized for the study.

Table4 Time and Events Table

	Visit Type	Clinic Visit	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Phone Call
	Study period	Screening	Treatment	Tre.itment	Treatment	**Treatment**	T reatment	Follow- up	Follow- up
	Study Day		1	3, 5	4/6•	15	29	91	181
	Visit Window (Days)	-5 to 1	0	2 days (-1/+1), 4 days (0/+2) after vacc	3/5 days (-1/+l) after vacc	14 da ys (-2/+2) after vacc	28 days (-7/+14) after vacc	90 da ys (-14/+14) **aftel' vacc**	180 days (-14/+14) after vacc
	Visit Number	Pre-**vacc.ination**	1	N/A	2	3	4	5	*6*
Stud y Event	Referen ces								
Study Treatment									
Vaccination (vacc)	Section 5.2		X						
Screening **and Safety**									
Informed Consent"	Section 5.1.1	**X**							
Medical HistOJY	Section *5*.1.2	**X**							
Physical Exam	Sections *5*.1.2 and 5.3.1	**X**	**X<**		**X**		**X**		
Pregnancy Test	Sections 3.5 and 5 .1.2	**X**	**X<**						
Exclusion/Inclusion Criteriad	Section4	**X**	**X**						
Randomization	Section 5.1.4		**X<**						
30 Minutes Post InjectionAssessment	Section *5*.2.1		**X**						

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	Visit Type	Clinic Visit	Clinic Visit	**PhoneCall**	Clinic Visit	**Phone Call**	Clinic **Visit**	**Phone** Call	**Phone Call**
	Study **period**	**Screening**	**Treatment**	**Tre.itment**	**Treatment**	**Treatment**	**Treatment**	**Follow-up**	**Follow-up**
	Study Day		**1**	3, 5	**4/6**	**15**	29	**91**	**181**
	Visit Window **(Days)**	-5 to **1**	0	2 days (-1/+l), 4 days(0/+2) **after vacc**	3/5 da)'S (-1/+l) **after** vacc	**14** da ys (-2/+2) **after vacc**	**28days** (-7/+14) **after vacc**	90days (-14/+14) **aftel' vacc**	**180** da ys **(-14/+14) after vacc**
	Visit **Number**	**Pre-vacc.ination**	**1**	**NIA**	2	3	**4**	5	***6***
Study Event	References								
SubjectDiary Dispensed with Training	Section 5.2.1		**X**						
SubjectDiary Reminder Call	Section 5.2.2			X'	X'				
SubjectDiary Reviewed and Collected	Section 5.3.1						X		
Assess Unsolicited AEs	Section7.1		**X**		**X**	**X**	X		
Assess SAEs	Section 7.1.4		**X**		**X**	**X**	X	X	X
Assess for medically attended AEs and AEs leading to withdrawal	Sections 7.I.4.I and7.1.3		**X**		**X**	**X**	X	X	X
Assess relevant medications/ vaccinations	Sections5.1.2 and 6.5	X	**X**		**X**	**X**	X	X	X

Visit Type		Clinic Visit	Clinic Visit	**PhoneCall**	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Phone Call
Study period		Screening	**Treatment**	**Tre.itment**	**Treatment**	**Treatment**	**Treatment**	Follow- up	Follow- up
Study Day			1	3, 5	4/6	15	29	91	**181**
Visit Window (Days)		-5 to 1	0	2 days (-1/+1), 4 da ys (0/+2) after vacc	3/5 da)'S (-1/+1) after vacc	14 days (-2/+2) after vacc	28days (-7/+14) after vacc	90days (-14/+14) **aftel' vacc**	180 days (-14/+14) after vacc
Visit Number		Pre- **vacc.ination**	1	NIA	2	3	**4**	5	***6***
Study Event	References								
Imm unogenicity									
Serology blooddraw	Section 3.5		X"		X		X		
Study C-0mp lerion **Pt·ocedure**									
Study Tenninatiorn	Sec tion *5.5*								X

Notes :

- Subject will be randomized into a blooddraw schedule in a 1:1 ratio. The second clinic visit will occur at Day 4 OR Day *6*.

b Confirm consent fonn(s) signed prior to any procedures.

' Procedure to be performed prior to vaccination

d Reminder for previously vaccinated subjects, appropriate written documentation of the identity of the primary meningococcal vaccination (Menveo or Menactra) and vaccination datemust be provided prior to enrollment.

- If the clinic visit at Day4is overlapping withthe specified window of the Day 3 reminder call, the Day 3 reminder call maybe omitted. If the clinic visit at Day *6* is overlapping with the specified window of the Day *5* reminder call, the Day *5* reminder call maybe omitted

f Subjects who tenninate thestudy early are recommended to complete certainstudy-related procedures. See section *5.5* for further details.

LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Imm1mization Practices
AE	Adverse Event
CI	Confidence Inteival
CBER	Center for Biologics Evaluation and Research
CRM	Cross Reactive material
CRO	Contract Research Organization
EC	Ethics Committee
EoS	End of Study
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
GSK	GlaxoSmithKline Biologicals
HIPAA	Health Insurance Portability and Accountability Act
hSBA	Human Serum Bactericidal Assay
IB	Investigator' s Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IM	Intramuscular
IRB	Institutional Review Board
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
pp	Per Protocol
Ref.	Reference
SAE	Serious Adverse Event
SDAF	Source Documentation Agreement Form
SBIR	Source Data Base for Internet Randomization
SOC	System Organ Class
SOP	Standard Operating Procedure

l. BACKGROUl"-D M 'D RATIONALE

1.1 Background

Neisseria meningitidis is a leading cause of bacterial meningitis and sepsis worldwide, capable of causing outbreaks and epidemics of invasive disease. Meningococcal disease is associated with high morbidity and mortality even among patients who receive early antibiotic treatment. Most cases of invasive disease worldwide are caused by serogroups A, B, C, W and Y.

The quadrivalent meningococcal oligosaccharide diphtheria CRM-197 conjugate vaccine (MenACWY-CRM; Menveo, GSK Biologicals) is approved for active irom1mizati.on of individuals from 2 months through 55 years of age in the United States. As of February 2015, more than 30,000 of subjects have been exposed to MenACWY-CRM vaccine in completed clinical studies and more than 24 million doses of the vaccine have been distributed globally.

The US Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination with a quadrivalent conjugated meningococcal vaccine for adolescents at 11-12 years of age with a booster dose administered 5 years later. While a substantial body of data exists showing a robust immune response and good antibody persistence after a single dose of MenACWY-CRM in adolescents, the response to a booster dose of MenACWY-CRM in this age group has only been evaluated in 2 clinical studies with limited number of subjects.

A robust anamnestic immune response to a booster dose of Menveo vaccine administered at approximately 5 years after previous vaccination with the same vaccine or a licensed meningococcal polysaccharide vaccine (Menomune®) was demonstrated in the phase 2 clinical study V59P6El . High titers of bactericidal antibodies against the vaccine serogroups were achieved at 7 and 30 days after booster dose in MenACWY-CRM-primed subjects. However, the number of subjects included in this study was relatively small (N=101, including 50 subjects who received a booster dose after the primary MenACWY-CRM vaccination).

In the phase 3b clinical study V59Pl3 El , a booster dose of MenACWY-CRM was given 3 years after primary vaccination with either MenACWY-CRM or Menactra®(a meningococcal diphtheria toxoid-conjugated MenACWY vaccine, MenACWY-D) in adolescents. A booster dose was able to substantially increase antibody titers against all 4 serogroups irrespective of the priming vaccine. Again, only small number of subjects (N=160) received the MenACWY-CRM booster, (83 who received primary MenACWY-CRM and 77 who received MenACWY-D).

In the light of the current ACIP recommendation for a booster dose of MenACWY-CRM, there exists a need to evaluate the response to a MenACWY-CRM booster given at - 5 years after primary vaccination in meningococcal-vaccine primed adolescents. Generation of this data would also be of relevance in outbreak management and vaccination of travelers to endemic areas.

1.2 Rationale

The pwpose/aim of this study is to assess the safety and antibody response to vaccination with a booster dose of Menveo given 4-6 years after primary vaccination and the response to a single dose given to vaccine-naive subjects, and to describe the inunune response over time after a booster dose of Menveo, administered to subjects previously vaccinated with Menveo or Menactra, and after a single dose of Menveo to vaccine-naive subjects. The inclusion of vaccine-naive subjects in a separate study arm is to enable comparison of the rapidity and magnitude of an anamnestic response to a booster dose (in primed individuals) or the primary response to a first dose (in naive individuals) of MenACWY-CRM.

2. OBJECTIVES

2.1 Plimary Objective(s)

Immunogenicity objective:

1. To demonstrate a sufficient immune response following a booster doseof MenACWY-CRM (Menveo) vaccine, given to subjects who previously received Menveo, as measured by the percentage of subjects with hSBA seroresponse[1] against *N. m.eningitidis* serogroups A, C, W and Y at Day 29 after vaccination
2. To demonstrate a sufficient immune response following a booster doseof MenACWY-CRM (Menveo) vaccine, given to subjects who previously received Menactra, as measured by the percentage of subjects with hSBA seroresponse[1] against ***N.*** *m.eningitidis* serogroups **A,** C, W and Y at Day 29 after vaccination

   Criteria to demonstrate immune response sufficiency The immune response sufficiency will be tested sequentially; first in the group of subjects who received primary vaccination with Menveo and, if met, also in the group of subjects who received primary vaccination with Menactra . The immune response will be considered as sufficient if the lower limit of the one-sided 97.5% CI for percentage of subjects with hSBA seroresponse[1] against serogroups A, C, Wand Y isgreater than 75%. The study will be considered successful if the immune response sufficiency will be demonstrated at least in the groupof subjects who received primary vaccination with Menveo.

2.2 Secondary Objective(s)

Secondar y Immunogenicity objectives:

1. To compare the immune responses over tinie following a booster doseof MenACWY-CRM vaccine, between subjects who previously received Menveo, subjects who previously received Menactra, and subjects who previously received Menveo or Menactra (pooled vaccine group) and following a single dose in vaccine-naive individuals, as measured by the percentages of subjects with hSBA

[1] Seroresponse is defined for thisstudyasfollows: For subjects with pre-vaccinationtiters <4, pos-t vaccination titers 2: 16; for subjects with pre-vaccinationtiters 2::4, post vaccination titers at least 4 timesthe pre-vaccination titers.

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seroresponse1, hSBA titers 8 and ;,:16 , and hSBA GMfs against *N. meningitidis* serogroups A, C, Wand Y at Day I, Day 4, Day 6, and Day 29 after vaccination.

2. To assess persistence of bactericidal antibodies against serogroups A, C, Wand Y at approximately 4-6 years after the primary vaccination with Menveo and after the primary vaccination with Menactra in comparison with naturally-acquired level in vaccine-naive individuals, as measured by the percentages of subjects with hSBA titers 8 and hSBA GMfs at Day 1.

Secondar y Safety objectives:

To assess the reactogenicity and safety of MenACWY-CRM vaccine when administered to subjects who previously received Menveo or Menactra and vaccine-naive individuals.

2.3 Explor atory Objective(s)

There are no exploratory objectives.

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3. STUDY DESIGN

3.1 Overview of Study Design

This is a phase 3b, controlled, open-labe multi-center studyto evaluate safety and immunogenicityof MenACWY-CRM after a single vaccination in healthy individuals who were vaccinated with Menveo or Menactra 4 to 6 years before and in vaccine-naive individuals.

Study population: Approximately 700 healthy subjects 15 through 55 years of age will be enrolled in the study.

Duration of the study The duration of this studyis approximately 6 months per subject.

Written informed consent and, as applicable according to local guidelines, written assent will beobtained before conducting any study-specificprocedures

Vaccination schedule: All subjects will receive a single dose of MenACWY-CRM at Day 1.

Study groups:

Group Menveo-Menveo: approximately 300 subjects, who were vaccinated with a single dose ofMenveo 4 to 6 years before, willreceive one dose of MenACWY-CRM.

Group Menactra-Menveo approximately 300 subjects, who were vaccinated with a single dose of Menactra 4 to 6 years before, will receive one dose of MenACWY-CRM.

Group Naive: approximately 100 subjects equally enrolled across all clinical sites, who have not received any meningococcal vaccination, willreceive one dose of MenACWY-CRM.

Randomization / Stratification:

Within each study group, subjects will berandomized into one of two different blood draw schedules according to a 1:1 ratio, described as follows:

- Subjects getting blood draws at Day 1, Day 4 and Day 29.
- Subjects getting blood draws at Day 1, Day 6 and Day 29.

For a schematic overview, see Table 1

Table 3.1-1: Schematic diagram of the VS9_77 study groups

Vacdne History	Vaccination in cwTent study	Blood draw schedule
Menveo N=300	Menveo	Blood draw Day1, 4, 29 (N=l 50)
		Blood draw Day 1, 6, 29 (N= l 50)
Menactra N=300	Menveo	Blood draw Day 1, 4, 29 (N=150)
		Blood draw Day 1, 6, 29 (N= l 50)
Vaccine-Naive N=IOO	Menveo	Blood draw Day I, 4, 29 (N=50)
		Blood draw Day I, 6, 29 (N=50)

Blinding: open-label study.

Blood sanmles: Three (3) blood samples of approximately 10 mL each will be collected according to the blood draw schedule in Table 3.1.1.

Data collection: Electronic Case Report Form (eCRF).

Study clinic visits: Three (3) clinic visits at Day I, Day 4 or Day 6 and Day 29 are planned for eachsubject.

Reminder Phone calls: Two (2) reminder phone calls willbe conducted at Day 3 and Day S after the study vaccination to remind the subject/legalguardian to complete the diary card.

Safety phone calls: Three (3) safety phone calls (at Day IS, Day 91 and Day 181) will be conducted to collect any medically-attendedAEs, AEs leading to withdrawal, SAEs, related medications and any vaccinations. In addition, all unsolicited AEs and related medications occurring after the vaccination willbe collected during the safety call at Day IS. The Day 181 Safety Phonecall will also serve as the termination visit.

Solicited Adverse Events (injection site pain, erythema, induration, fatigue, headache, myalgia, arthralgia, loss of appetite, nausea, chills and fever) occurring on the day of vaccination and the following six days (Day 1 through Day 7) willbe recorded daily using a Diary Card for all subjects.

Unsolicited AEs occurring within 28 days after studyvaccination will be collected. Qualified site staffwillinterview the subject by phone approximately 14 days after vaccination and in person at the studysite approximately 28 days after studyvaccination to assess the occUITence of any unsolicited AEs.

Medically-attendedAEs AEs leading to stuqy withdrawal and SAEs will be collected during the entire study period. These data will be captured by interviewing the subject and/or subjects' parents / guardian (as applicable) during the sitevisits and phone calls and by review of available medical records. Subjects and/or parents / guardian will be encouraged to call the site in the event of any medically-attendedAEs or any AEs which theyperceive as being of concern during the entire study period.

Table 3.1-2: Schematic diagram of the V59_77 study design

Day l	Da y 4	Da y 6	Da y 15	Da y 29	Da y 91	Da y 181
Blood draw (all subjects) Menveo	Blood draw (50¾of subjects)	Blood draw (50%of subjects)	Safety Phone call	Blood draw (all subjects)	Safety Phone call	SafetyPhone call Study termination

3.2 Study Period

Each subject should expect to participate in the study for 6 months, from the time of enrohnent through the last study visit.

3.3 Blinding Prncedures

The trialis designed as an open-label study.

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/Vaccinations
- Information on the blood samples

All data collected must only be identified using the Subject ID, as described in section S.1.4, Randomization.

3.4.2 Tools Used for Data Collection

Data willbe recorded in the Subject Diary and collected on electronic Case Report Forms (eCRFs).

Subject Diar y

Paper Diaries (pDiaries), hereafter referred to as Subject Diaries will be the onlysource document allowed for solicited local and systemic adverse events (including body temperature measurements), starting after the initial, 30minute post-vaccination period at the clinic. The following additional rules apply to documentation of safety information collected in the Subject Diary.

The Investigator or delegated staffshould monitor the Subject's Diary status throughout the study for compliance and anysolicited local and systemic adverse events that were of concernto the subject.

- No corrections or additions to the information recorded by the subject or parent(s)/legal guardian(s) within the Subject Diary willbe allowed after it is delivered to the site.
- Any blank or illegible fields on the Subject Diary must be described as missing in the eCRF.

Case Rep01t F or ms

This study utilizes electronic Case Report Fonns (eCRFs) to collect study-related data from each subject. A qualified site staff member(s) is required to enter subject data in the eCRFs in English based on the medical information available in each subject' s source record.

Data should be entered into the eCRF in a timely fashion following each subject's clinic visit, study procedure, or phone call. Each subject's eCRF casebook will be compared withthe 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.

The following additional rules apply to documentation of Subject Diary information collected in the eCRFs:

- The site must enter all readable entries in the Subject Diary into the eCRF, including those values that may be biologically implausible (e.g. bodytemperature: 400°C).
- Any illegible or implausible data should be reviewed with the subject and/or parent(s)/legal guardian(s). 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 eCRF (e.g., if the subject above confinns 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 eCRF).

- Any newly described safety infonnation (including a solicited adverse event) nrust not be written into the Subject Diary and nrust 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 eCRF.

3.5 Collection of Clinical Specimens

- Collected samples will beused for protocol mandated research and purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these tests, the maintenance or improvement of these tests, the development of new test methods, as well as making sure that new tests are comparable to previous methods and work reliably.
- It is also possible that future findings may make it desirable to use the samples acquired in this study for future research, not described in this protocol. Therefore, all subjects in countries where this is allowedwill be asked to give a specific consent to allow GSK or a contracted partner to use the samples for future research. Future research willbesubject to the laws and regulations in the USAand willonly be performed once an independent Ethics Committee or Review Board has approved this research.

Information on further investigations and their rationale can be obtained from GSK.

Any sample testing willbedone in line with the consent of the individual subject/subject's parent(s).

Refer also to the : Investigator Agreement, where it is noted that the investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

If additional testing is performed, the marker priority ranking given in the table below may be changed.

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

- Blood.

- Urine for pregnancy testing (As per routine practice, specimens willbetested at each site).

Processing of a specimen should be completed bya qualified site member and in accordance with the study-specificLaboratory Manua.l Testing of serum specimens will be performed bya GSK or a designated laboratory. Refer to the study-specificClinical Specimen Laboratory Manual for additional details.

Blood Specimens

Approximately 10 mL sample ofblood willbedrawn fromall subjects at visit Day 1 before vaccination, and at visit Day 4 or Day 6 and visit Day29. The blood volume will not exceed 10 mL at each time point in order to provide the necessary serum volume (approximately half of the blood draw volume) for the serology assays.

The blood will be used for immunological assays. See section 7, Assessments for additional details.

The total amount of blood collected over the study period per subject will be approximately 30mL.

U1in e S p eci m e ns

Urine willbe collected for pregnancy testing in females of child bearing potential. Urine will be collected at visit Day 1 before vaccination and the results recorded in the source document and eCRF.

3.6 Stopping/Pausing Guidelines

There are no predetermined stopping rules in this study. Subjects may be withdrawn from the study according to investigator discretion as described in section 3.8, Premature Withdrawal from Study.

3.7 Data Monitoting Committee

No DMC willbeutilized for the study.

3.8 Prema tur e \Vithdrawal 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 dministrative reasons. The investigator or study coordinator nrust 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 before or 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 S.5.1, Early Termination Visit 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.

AdverseEvent

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 eCRF page by indicating "Withdrawn from study due to AE". Any ongoing AEs at the time of studywithdrawal must be followed until resolution or stabilization

Death

For anysubject withdrawn fromstudy participation due to death, this should be noted on the StudyTermination eCRF page and the associated SAE that led to the death must be reported.

, v ithdrawal ofconsent

The subject and/or parent(s)/legal guardian(s) 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 and/or parent(s)/legal guardian(s) intends to withdraw consent from the study, the investigator should clarify if the subject will withdraw completely from the study or if the subject willcontinue 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.

If a subject and/or parent(s)/legal guardian(s) withdraws consent but does not revoke the HIPAA authorization, the Sponsor will have fullaccess to the subject's medical records, including termination visit information. If a subject and/or parent(s)/legal guardian(s) revokes only the HIPAA authorization, the Sponsor will have fullaccess to all of the subject's medical records prior to the date and time of written revocation.

Lost to Follow-Up

For subjects who fail to show up for finalvisits (clinic or telephone contacts), or for three consecutive visits, study staff are 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 and/or parent(s)/legal guardian(s) to encourage the completion of study teimination procedures. These efforts to contact the subject should be recorded in the source document. The termination date for the subject to be captured on the Study Termination eCRF page is the date of the last successful contact (clinic visit or telephone) withthe subject.

AdministrativeReason

Examples forsubjects withdrawn from the study due to administrativereason can include: Sponsor decision to terminate the study, subject discontinuation for insurance issues, moving, no time, etc. This reason should be noted in the StudyTermination eCRF page and any ongoing AEs at the time of studywithdrawal should be followed until resolution/stabilization, if possible.

If the clinical studyis prematurely terminated bythe 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/vaccine,setc.) 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 StudyTermination eCRF page.

Protoco l Devia tion

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 thesubject's health, safety, or rights.

Investigators will apply due diligence to avoid protocol deviation.sUnder 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 pennitted. If the investigator feels a change to the protocol would improve the conduct of the study this must be considered a protocol amendmen,tand unless such an amendment is agreed upon by GSK and approved by the IRB/EC and health authorities it cannot be implemented.

Anysubject who becomes pregnant during thestudy, despite the protocol requirement for adequate contraception should be encouraged to continue participating in the study for safety follow-up only. The site must complete a Pregnancy Report CRF (initial report) as soon as possible after learning of pregnancy occurrence (see section 7.1.6, Pregnancies for further details). If the subject withdraws fromthe study for any of the above categories except death, the site will obtain permission from the subject to continue to remain in contact with heruntil the outcome of the pregnancy is known, evenif the outcome is not known until after thesubject reaches theend of follow-up period.

3.9 End of Study

Most clinical trials intended to support the efficacy/immunogenicityand safety of an InvestigationalProduct proceed to full completionofplanned samplesize accrual. Forthe pwpose of this protocol, End of Study (EoS) is defined as the date of the last testing/reading released of human biologicals samples, related to primary and secondary end points, to be achieved no later than 8 months after Last Subject Last Visit (LSLV.)

If the completion of testing occurs prior the completion of the Last Subject Last Visit (LSLV) the latter date defines the end of study visit.

4. SELECTION OF STUDYPOPULATION

4.1 Inclusion C1iteria

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

I. Individuals of IS through SS years of age on the day of informed consent or assent.

2. Individuals who received Menveo 4 to 6 years prior to enrolment at an age of 11 years or older (Menveo-Menveo group)

   OR

   Individuals who received Menactra 4 to 6 years prior to enrolment at an age of 11 years or older (Menactra-Menveo group)

   OR

   Individuals who have not received any previous meningococcal vaccine (Naive group).

3. Individuals who have voluntarily given written informed consent (and/or assent, if applicable) after the nature of the study has been explained according to local regulatory requirements, prior to study entry. If the subject is under age 18 at the time of enrolment, the parent(sJ/legal *guardian(s)* of the subject should have voluntarily given written informed consent.

4. Individuals who can comply with study procedures including follow-up[1] .

S. Males

   Or

   Females of non-childbearing potential[2]

   Or

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[1] A subject and/or parent(s)/Jegal guardian(s) is/are considered to be compliant if the Investigator judges that the subject will complete the Subject Diary and return for all the follow-up visits scheduled in the study.

[2] A female is considered to be of non-childbearing potential prior to menarche and after natural or induced menopause. Natural menopause is recognized to have occurred after 12 consecutive months of amenorrhea for which there is no other obvious pathological or physiological cause. Induced menopause is recognized to have occurred after hysterectomy, after bilateral oophorecotmy, or iatrogenic ablation of ovarian ftmction.

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Females of childbearing potential who are using an effective birth control method[1] which they intend to use for at least 30 days after the study vaccination

4.2 Exclusion Crite1i a

Each subject must not have:

1. History of any meningococcal vaccine administration other than the single vaccination given 4 to 6 years before (Menveo-Menveo and Menactra-Menveo groups)

   OR

   History of any meningococcal vaccine administration (Naive group).

2. Current or previous, confirmed or suspected disease caused by *N. meningitidis*.
3. Household contact with and/or intimate exposure to an individual with any laboratory confirmed *N. meningitidis* infection within 60 days prior to study vaccination
4. Progressive, unstable or \lllcontrolled clinical conditions.

S. Hypersensitivity, including allergy, to any component of vaccines, medicinal products or medical equipment whose use is foreseen in this study.

6. Clinical conditions representing a contraindication to intramiscular vaccination (IM) and blood draws.
7. Abnormal function of the immllllle 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 study vaccination
   c. Administration of antineoplastic and immllllomodulating agents or radiotherapy within 90 days prior to study vaccination

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[1] The following birth control methods are considered effective:
Abstinence
Hormonal contraceptive (such as oral, injection, transdennal patch, implant) if used for at least 30 days prior to informed consent
Diaphragm preferably with spermicide, tubal occlusion device
Intrauterine device (IUD)
Tubal ligation
Male par1ner using condom preferably with spermicide
Male par1ner having been vasectomized at least six months prior to informed consent

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8. Received immunoglobulins or any blood products within 180 days prior to informed consent.
9. Received systemic antibiotic treatment (PO/IV/IM) within 3 days prior to study vaccination or blood draw.
10. Received an investigational or non-registered medicinal product within 30 days prior to study vaccination.
11. Study personnel as an immediate family or household member.
12. Individuals who have received any other vaccines within 7 days (for inactivated vaccines) or 14 days (for live vaccines) prior to vaccination in this study or who are planning to receive any vaccine within 28 days from the study vaccination.
13. Individuals who have experienced a moderate or severe acute infection and/or fever defined as a temperature 38°C (100.4°F) within 3 days prior to study vaccination.
14. Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the subject due to participation in the study.

4.3 C1ite1ia for De.lay of Vaccination and/or Blood Sampling

There may be instances when individuals meet all eligibility criteria for vaccination yet have a transient clinical circumstance which may warrant delay of vaccination: body temperature elevation [38.0° C 100 .4° F) within 3 days prior to intended study vaccination], systemic antibiotic treatment within 3 days prior to study 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.

There is a clinical circumstance that warrants delay of blood collection for immunogenicityassessments in this study subject has received a dose of systemic antibiotics less than 3 days before the intended blood collection. In the event that a subject meets this criterion for delay of blood collection, blood collection may proceed once the window for delay has passed.

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5. 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 Table4.

Table 5-1 Study Procedures

Visit Category	Procedures
Pre-vaccinationClinic Visit(s)	Section 5.1 describes procedures to be followed priorto study vaccination: informed consent/assent, screening, enrolment, andrandomization
VaccinatiooClinic Visit(s)	Section5.2 describesprocedures tobe followed duringeachclinic visitinvolvingvaccination: vaccination, post-vaccination procedures, and post-vaccination reminders
Post-vaccination Visit(s)	Section5.3 describes follow-upclinic visitsand safety follow-up calls
Unscheduled Visit(s)	Section 5.4 Unscheduled visits are not expected withinthis protocol.
Study Termination Visit	Section5.5 describes procedures to be followed at the last study visit for a subject (may include early termination visit)

5.1 Pre-vacc ination Clinic Visit.(s)

This section describes the procedures that must be performed for each potential subject prior to vaccination, including obtaining informed consent/assent, screening, enrolment and randomization.

5.1.1 Informed Consent/Assent

"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 willof 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.

"Assent" is a term used to express willingness to participate in research by persons who are by definition too young to give informed consent but who are old enough to

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understand the proposed research in general, its expected risks and possible benefits, and the activities expected of them as subjects. Assent by itself is not sufficient, however. If assent is given, informed consent must still be obtained from the subject's parent(s) or legal guardian(s). Local laws define who constitutes a "child," and such definitions dictate whether or not a person can legally consent to participate in a protocol (Levine 1988).

Info11lled consent of the parent(s)/legal guardian(s) and assent of subject following local IRB/EC guidance **must** be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent and assent should be documented in the subject source document in addition to maintaining a copy of the signed and dated informed consent. Additional specifics regarding the informed consent and assent processes are located in section 13.2, Info11lled Consent Procedures.

If a subject and/or parent(s)/legalguardian(s) is unable to read, an impartial witness should be present during the entire informed consent and assent discussion. An impartial witness is defined as a person who is independent from study conduct, who cannot be unfairly influenced by those involved with the study, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject and/or parent(s)/legal guardian(s) and after the subject and/or parent(s)/legal guardian(s) has verbally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the informed consent fo11ll, the witness should sign and personally date the consent form. By signing the consent fo11ll, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject and/or parent(s)/legal guardian(s) and that informed consent was freely given by the subject and/or parent(s)/legal guardian(s).

5.1.2 Screening

Subject identification numbers will be assigned sequentially to the subjects who have consented to participate in the study, according to the range of subject identification numbers allocated to each study center. The eligibility of the subject will be determined based on the inclusion and exclusion criteria listed in section 4, Selection of Study Population and evaluated during this screening procedure.

Prior to study enrolment, demographic data will be collected from the subject, including: date of birth, gender, race, ethnicity, prior vaccination against meningitis. Note: Appropriate written documentation of the brand of primary vaccination (Menveo or Menactra) and vaccination date must be provided prior to enrollment.

Medical history willalso be collected, including but not limited to any medical history that may be relevant to subject eligibility for study participation such as prior vaccinations, concomitant medications, and previous and ongoing illnesses or injuries. 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.

Review of systems is a structured interview that queries the subject and/or parent(s)/legal guardian(s) as to any complaints the subject has experienced across each organ system This will beperformed before enrolment and used to guide physical examination.

If applicable, prior and concomitant medications or vaccinations taken prior to start of study should be collected (refer to section 6.5, Prior and Concomitant Medications and Vaccines for further details).

Collect vital signs (heart rate, blood pressure, and temperature (preferably taken orally). Measure height and weight.

Perform pregnancy testing in women of childbearing potential (refer to section 3.5, Collection of Clinical Specimens for additional information)

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.

The data collected through study assessments listed above willbewritten in the source document (see section 9.1, Source Documentation). Should the physical assessment reveal any abnormal values or events, these must be documented in the CRF Adverse Events Form

Prior to vaccination, approximately 10 mL of blood will bedrawn from all subjects for the immunological testing see section 3.5, Collection of Clinical Specimens.

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 willbeenrolled into the study.

5.1.3 Em·olment

After signing the informed consent, if an individual is determined to be eligible for study participation, the investigator will enroll the subject and enter the subject information into randomization system, Source Data Base for Internet Randomization (SBIR).

5.1.4 Randomization

5.1.4.1 Randomization of supplies

The randomization of supplies within blocks will be performed at GSK, using MATerial EXcellence (MATEX), a program developed for use in Statistical Analysis System (SAS®) (Cary, NC, USA) by GSK. Entire blocks will be shipped to the study centre.

5.1.4.2 Study group and tJ·ea tm e n t numb e r all oc a tio n

Enrolled subjects willbe randomized in the SBIR system to one of two different blood draw schedules according to a 1:1 ratio, described as follows:

- Subjects getting blood draws at Day 1, Day 4 and Day 29.
- Subjects getting blood draws at Day 1, Day 6 and Day 29.

Allocation of the subject to a blood draw schedules at the investigator site will be performed using a central randomization system on internet (SBIR).

The randomization algorithm will use 3 minimizationprocedure accounting for the previous vaccination status (Menveo, Menactra or Vaccine-Nai'vestudy group).

For each dose, the study staffin charge of vaccine administration will access SBIR, provide the subject ID, and the system will provide a treatment number consistent with the allocated treatment arms.

SBIR will also be used to ensure adequate and appropriate distribution of enrolment of naivesubjects across all sites.

For any question regarding SBIR, please refer to the SBIR user guide and SBIR Manual for specific instructions. 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 and 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 Documentation Agreement Form (SDAF). The information on subjects who are randomization failures should be

kept distinct from subjects who are screen failures, as described in section S.1.2, Screening.

If for any reason, after enrolment the subject fails to undergo treatment/study procedures this is an Early Termination and the reason should be recorded in source document as specified in the Source Documentation Agreement (SD.AF). The information on these Early Termination subjectsshould be kept distinct in the source documentation from subjects who are screen failures, as described in section 5.1.2, Screening.

5.2 Vaccination Clinic Visit

The first vaccination will be performed on Day 1.

For studies which have visits for concomitant vaccinations or treatments, see section 6.5, Prior and Concomitant Medications and Vaccines for those visit procedures.

Ensure all blood samples are taken **p1i or** to the vaccination .

After completing the pre-vaccination procedures on day 1, administer the vaccine to the subject according to the procedures described in section 6.3, Vaccine Preparation and Administration. Observe the blinding procedures described in section 3.3, Blinding Procedures.

Prior to administrationof study vaccination, confirm that the subject does not meet any criteria for delaying additional study vaccinations as described in section 4, Selection of Study Population.

5.2.1 Post-vaccination Procedures

The following post-vaccination procedures will be performed on day 1.

- After vaccination, the subject willbe observed for at least 30 minutes including observation for unsolicited adverse events, solicited adverse events, and body temperature measurement. Record all safetydata collected during this time in the subject's source document.
- A Subject Diary will be used in this studyto document solicited adverse events. The Subject Diary is the only source for collection of these data; therefore, it is critical that the subject completes the Subject Diary correctly. The subject should be trained on how and when to complete eac!J field of the Subject Diary.
- The subject and/or parent(s)/legal guardian(s) should be trained on how to self-measure localsolicitedadverse events. The measurement of solicited local adverse events is to be performed using the ruler provided by the site.

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- The subject and/or parent(s)/legal guardian(s) should be instructed how to perform bodytemperature measurement using the thermometer provided by the site.If the subject feels unusually hot or cold during the day, the subject and/or parent(s)/legal guardian(s) should check body temperature. If the subject has fever, the highest body temperature observed that dayshould 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 and/or parent(s)/legal guardian(s), but if a person other than the subject and/or parent(s)/legal guardian(s) enters information into the Subject Diary, this person's identity must be documented in the Subject Diary or subject' s source record. Any individual that makes entries into the Subject Diary must receive training on completion of the Subject Diary at the time of the visit. This training must be documented in the subject's source record.

The same individual should complete the Subject Diary throughout the course of the study.

- The site should schedule the next study activity clinic visit on Day 4 or Day 6 depending to which blood draw schedule subject was randomized to with the subject and/or parent(s)/legalguardian(s).

The subject and/or parent(s)/legal guardian(s) will be reminded to complete the Subject Diary and to contact the site if there are any questions, and to contact the siteimmediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency roomvisit or to a visit to/by a doctor or is of concern.

5.2.2 Post-vaccination Reminders

Reminder calls or alerts are not intended to be an interview for collection of safety data. If the subject and/or parent(s)/legal guardian(s) wishes to describe safety information, this information should only be collected by a healthcare professional at the site, and the safety data described must be written down in the subject's medical chart.

Subject Diary Reminder Calls

Subject Diary reminder calls will be performed on day 3 and day S. The purpose of this callis to remind the subject and/or parent(s)/legal guardian(s) about completion of the Subject Diary. The call follows the Subject Diary Reminder Telephone Call Script provided to the site. The subject and/or parent(s)/legalguardian(s) should be reminded to contact the site via the telephone number provided in the informed consent to discuss

medical questions. If the clinic visit at Day 4 or Day 6 overlaps with the specified window of the Day 3 or Day 5 reminder call, the Day 3/Day 5 reminder call maybe omitted.

5.3 Post-vaccination Visit(s)

Post-vaccinationvisits willbe performed on Day 4 or Day 6 according to the blood draw schedule to which subject was randomized and Day 29.

5.3.1 Follow-up Clinic Visit(s)

Follow-up clinic visits willbe performed on Day 4 or Day 6 according to the blood draw schedule to which subject was randomized and on Day 29. During the follow-up clinic visit:

- Subject Diary willbe reviewed at Day 29. No changes to the information recorded within the Subject Diary are permissible. For details on the Subject Diary see sections 3.4.2, Tools Used for Data Collection and 5.2.1, Post-vaccinationProcedures. The subject and/or parent(s)/legal guardian(s) 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. This interview will follow a script which will facilitate the collection of relevant safety information. 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. Adverse events reported by the subject and/or parent(s)/legal guardian(s) at this follow-up clinic visit must be recorded in the subject's source document and on an Adverse Events CRF, as specified in section 7.1, Safety Assessment, and not written on the script used for the interview.
- Perform a brief symptom-directed physical examination if necessary according to symptoms the subject has reported. This is a physical examination that will include an examination of organ systems that are relevant to the investigator based on review of the subject's reported adverse events and concomitant medication use. This assessment may include: measurement of vital signs, bodytemperature and a check of general appearance. The physical assessment must be performed by the investigator or designee of the investigator, who is qualified to perform a physical assessment in accordance with their institutional policy. Corresponding information is documented in the subject's source document and CRF(s).
- Collect a blood sample (see section 3.5, Collection of Clinical Specimens for additional information).

The site should schedule the next study activity safety call withthe subject and/or parent(s)/legal guardian(s).

Thesubject and/or parent(s)/legal guardian(s) will receive a written reminder of the next planned study activity. The subject and/or parent(s)/legal guardian(s) 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 hospitalizationor an emergency roomvisit.

5.3.2 Safety Follow-upCalls

Safety follow-up call will be performed on Day 15, Day 91 and Day 181.

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 and/or parent(s)/legalguardian(s) will be interviewed according to the script, and information related to unsolicited adverse events (only at Day 15), serious adverse events (SAEs), medically attended adverse events, AEsleading to withdrawal and concomitant medications or vaccinations associated with those events will be reviewed. 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.

Thesite should schedule the next study activity with the subject and/or parent(s)/legal guardian(s).

The subject and/or parent(s)/legal guardian(s) 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 hospitalizationor an emergency room visit.

5.4 Unscheduled Visits

Unscheduled visits are not expected within this protocol.

5.5 Study Termination Visit

The study termination visit willoccur on Day 181. The termination visit will be a telephone call. The date of termination is the date of the last contact (clinic visit or telephonecall) 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, Early Termination Visit.

During the telephone call, the following procedures will be performed: interview of subject and/or parent(s)/legal guardian(s) to collect medically attended adverse events, AEs leading to withdrawal, SAEs, as well as interview of subject and/or parent(s)/legal guardian(s) to collect concomitant medications/ vaccinations associated with those events. All safety infollillltiondescribed 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 will review with the subject and/or parent(s)/legal guardian(s) the plan of when infonnation 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 and/or parent(s)/legalguardian(s) chooses to share this infonnation.

The site willcomplete 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 notifythe Sponsor and, when possible, will perform the procedures listed below. The reason(s) for the early termination will be included in the subject's source documentation. If the EarlyTermination Visit is a telephone call, collect as muclt 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 will be performed: interview of subject and/or parent(s)/legal guardian(s) to collect adverse events, medically attended adverse events, AEs leading to withdrawal, SAEs, interview of subject and/or parent(s)/legalguardian(s) to collect concomitant medications/ vaccinations.

The site will review with the subject and/or parent(s)/legal guardian(s) the plan of when infonnation 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 and/or parent(s)/legalguardian(s) chooses to share this infonnation.

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

6. TREATME1''TOF 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 associa ted with this study must be checked for expir ation date plior 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 below. The study vaccines specific to this study is the MenACWY-CRM vaccine (Menveo®, GSK Biologicals).

The Meningococcal ACWY conjugate vaccine is obtained by extemporaneous mixing just before injection of the lyophilized MenA-CRM component with the MenCWY-CRM fullliquid vaccine. The pharmaceutical form is Powder and solution for solution for injection. Menveo® is provided as vial/vial presentation. MenA lyophilised conjugate component (glass vial) and MenCWY liquid conjugate component (glass vial). After reconstitution, MenACWY-CRM will have the following composition per O.S mL of injectable solution (SeeTable6.1-1):

Table 6.1-1: MenAC\VY-CRM Composition

Name of Ingredient	Unit and/ol' Percentage Fol'mula (Dose 0.5 mL)
Dl1gSubstances	
CRM191-MenA conjug;ite	10 µg MenA,16.7- 33.3µgCRM191
CRM191-MenCconjug;ite	5 µgMenC, 7.1 - 12.5 µg CRM197
CRM191-MenWconjugate	5 µg MenW, 3.3- 8.3µgCRM191
CRM191-MenYconjug;ite	5 µg MenY, 5.6- 10µgCRM197
Sodium chloride	4.5mg
Excipients	
Sucrose	12.5 mg
Sodium phosphate buffer Sodium dihydrogen phosphate Disodium hydrogen phosphate dehydrate	l0mM 2.5mM 7.5mM
Potassium dihydrogen phosphate	5mM
Water for Injection	q.s 0.5 mL
VolumeofFormulation	0.6mL

Name of Ingredient	Unit and/ol' Percentage Fol'mula (Dose 0.5 mL)
Appearance	Colorlesstolight yellow
Vaccine Presentation	Asingle dose of two vials

One 0.5 mL dose ofMenACWY will be administered by intranruscular (IM) injection in the deltoid area of non-dominant arm (preferably.)

For more detailed information, refer to the latest version of Investigator Brochure and SPC for Menveo® , which are included in the investigator site file.

6.2 Non-Study Vaccines

Not applicable.

6.3 Vaccine Preparation and Administration

The investigator or designee will beresponsible 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 onlyby personnel who are qualified to perform that function under applicable local laws and regulations for the specific study site.

All studyvaccines to be administered to the subjects must be stored in a safe and locked place with no access by unauthorized personnel.

The study vaccines will be stored at the defined temperature range (i.e. +2 to +8 C). The storage temperature of the vaccines will be monitored daily withtemperature monitoring devices andwillberecorded.

Any temperature deviation, i.e. temperature outside the range (+2 to +8°C), must be reported to thesponsor as soon as detected. Following the exposure to such a temperature deviation, vaccines will not be used until written approval has been given by the sponsor.

The study vaccine should be allowed to reach room temperature before administration, according to local vaccination practice.

MenACWY-CRM (Menveo) vaccine is prepared by aseptically withdrawing all fluid fromthe vial containing the MenCWY-CRM liquid conjugate component and injecting the liquid into the vial containing the MenA-CRM lyophilized portion. Invert and shake the vial well until the vaccine is dissolved. The finalmixed vaccine is then ready for administrationof the MenACWY formulation (0.5 mLJdose of injectable solution).

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Detailedvaccinepreparationandadministrationinstructionswillbeprovidedto investigators in the Clinical Trials Supply Manual prior to study start.

PRECAUTIONS TO BE OBSERVED IN ADMINISTERINGSTUDY VACCINE:

Prior to vaccination, subjects must be determined to be eligible for studyvaccination and it must be clinically appropriate in the judgment of the investigator to vaccinate. Eligibilityfor vaccination prior to first study vaccine dministration is detennined by evaluating the entry criteria outlined in protocol sections 4.1, Inclusion Criteria and 4.2, Exclusion Criteria.

Eligibility for non-study vaccines should be determined by the investigator, pending the review of the package insert of the relevant vaccine.

Study vaccines should not be administered to individuals with known hypersensitivity to anycomponent of the vaccines.

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from fainting.

Standard immunization practices are to be observed and care should be taken to administer the injection intramuscularly. Before dminist"'1'ingvaccine, 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 should 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.

6.3.1 Replacement of unusable vaccines

In addition to the vaccine doses provided for the planned number of subjects (including extra doses to allow flexibility in enrolment at the different sites), at least 15% additional vaccine doses willbe supplied to replace those that are unusable.

6.4 Vaccine Adminish·ation Error or Overdoseof Vaccine

Vaccine administration error is defined as receiving a dose of studyvaccine that was not reconstituted as instructed or administered by a different route from the intended route of administration. An overdose of studyvaccine (whether accidental or intentional) is

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defined when a dosage higher than the recommended dosage is administered in one dose of study vaccine.

6.5 Plior and Concomitant Medications and Vaccines

All medications, vaccines and blood products taken or received by the subject within 30 days prior to the start of the study are to be recorded on the Prior and Concomitant Medications CRF.

In addition, the following are considered prior medications for this protocol: all medication/vaccines described in the inclusion and exclusion criteria of this protocol including:

- Systemic administration of corticosteroids (PO/IV/IM) for more than 14 consecutive days within 90 days prior to study vaccination;
- Administration of antineoplastic and imm1momodulating agents or radiotherapy within 90 days prior to study vaccination;
- Tmmnnnglobulins or any blood products within 180 days prior to informed consent;
- Systemic antibiotic treatment within 3 days prior to study vaccination or blooddraw;
- Any investigationalor non-registered medicinal product within 30 days prior to study vaccination;
- Administration of vaccines within 7 days (for inactivated vaccines) or 14 days (for live vaccines) prior to vaccination in this study or who are planning to receive any vaccine within 28 days from the study vaccination

Use of analgesics/antipyreticsto prevent or treat solicitedAEs will be captured in the Subject Diary from day 1-7 following each vaccination. 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.

Concomitant medications include all prescription and non-prescription medications (including vaccines) taken by/administered to the subject during the 30 days after study vaccination and must be documented on the Concomitant Medications CRF. Mineral supplements and vitamins are not considered concomitant medications.

When recording concomitant medications/vaccine,sthey should be clJecked against the study entry and continuation criteria in section 4, Selection of Study Population to ensure that the subject should be enrolled/continue in the study.

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Concomitant medication dministered for treatment of AEs with medically-attended visits, AEs leadingto study withdrawal andSAEs must be documented during the entire study period.

Any vaccine not foreseen in the studyprotocol in the period starting at Day1 and ending at Day 181 must be recorded in the eCRF.

6.6 Vaccine Supply, Labeling, Storage and Tracking

Detailed vaccine supply, labeling, storage and tracking instructions will be provided to investigators in the Clinical Trials Supply Manual prior to study start.

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7. ASSESSMENTS

7.1 Safety Assessment

The measures of safety used in this study areroutine clinical procedures. They include a close vigilance for, and stringent reporting of, selected local and systemic adverse events routinely monitored in vaccine clinical studies as indicators of reactogenicity.

An adverse event (AE) is defined as anyuntoward 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 withthis treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnonnal 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 defintiion includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

The period of observation for AEs extends fromthe time the subject signs informed consent until he or she completes the specified safety follow-up period of 180 days 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 source document. However, any AEs occurring prior to receipt of anystudyvaccine 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 arederived from organized data collection systems, such as Subject Diaries.

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 and/or parent(s)/legalguardian(s) for 7 consecutive days, using a pre-defmed Subject Diary.

The following solicited adverse events are included in the Subject Diary. Each adverse event is to be assessed using the scoring system reported in parentheses below:

Solicited Local AdverseEvents

Injection sitepain, erythema, induration

Solicited Systemic Adverse Events

Fatigue, headache, myalgia, arthralgia, loss of appetite, nausea, chills, and fever.

Table 7.1.1-1 Severity grading for solicited local and systemic AEs

	]',fil d	**Moderate**	**Se.vel'e**
Pain	No inteiference with dailyactivity	Inteifereswith daily activity	Prevents daily activity
Erythema	25-50mm	51- lOOmm	> l OOmm
lnduration	25-50 mm	51- lOOmm	> l OOmm
Fatigue	No inteiference with dailyactivity	Inteiferes with daily activity	Prevents daily activity
Headache	No inteiference with activity	Inteiferes with daily activity	Prevents daily a activity
Myalgia	No inteiference with activity	Inteiferes with daily activity	Prevents daily activities
Arthralgja	No inteiference with activity	Inteiferes with daily activity	Prevents daily activity
Loss ofappetite	Eating less than usual with no effect on normal activity	Eating less thanusual / inteifered with normal activity	Not eating at all
Nausea	No inteiference with dailyactivity	Inteiferes with daily activity	Prevents daily activity
Chills	No inteiference with activity	Inteiferes with daily activity	prevents daily activity

Fever is defined and measured by a body temperature 38.0°C(100.4°F) Route of temperature measurement is preferably oral.

Other Indicators of Reactogenicity:

- Use of analgesics / antipyretics for prophylaxis (Days 1-7)
- Use of analgesics / antipyretics for treatment (Days 1-7)
- Body temperature, described in degrees Celsius and summarized by route of measurement and in *05°C* increments from 36.·o c .

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The study staff must review the data entered into the Subject Diary as described in section 3.4.2, Tools Used for Data Collection and section S.3.1, Follow-up Clinic Visit(s).

Note: Anysolicited adverse event that meets any of the following criteria must be entered into subjects' source document (see section 9.1, Source Documentation) and also as an adverse event on the Adverse Event CRF:

- Solicited local or systemic adverse event that continues beyond day7 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, Evaluation of Adverse Events).
- 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, Evaluation of Adverse Events).
- Solicited local or systemic adverse event that otherwise meets the definition of a serious adverse event (see section 7.1.4, Serious Adverse Events).

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 commtmicated bya subject and/or parent(s)/legal guardian(s) who has signed the informed consent.

Potential unsolicited AEs may be medically attended (defined as symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a health care provider,) or were of concern to the subject and/or parent(s)/legal guardian(s). In case of such events, subjects and/or parent(s)/legal guardian(s) will be instructed to contact the site as soon as possible to report the event(s). The detailed information about the reported unsolicited AEs willbe collected by the qualified site personnel during the interview and will be documented in the subject's records.

Unsolicited AEs that arenot medically attended nor perceived as a concern by subjects and/or parent(s)/legalguardian(s) will be collected during interview with the subject [and/or parent(s)/legalguardian(s) and by review of available medical records at the next visit (see section 5.3, Post-vaccination Visit(s).

7.1.3 Evaluation of Adverse Events

Adverse events, reported at a clinic visit or at a scheduled safety call, should be recorded in the eCRF verbatim, as reported by the subject.

Theseverity of events reported on the Adverse Events CRF willbe determined by the investigator as:

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

The relationship of the studytreatment 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 administrationof 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 studytreatment to an unsolicited AE will be determined by the investigator.

Note: solicited AEs will not be evaluated for relationship to studytreatment. Grading for severity of solicited local and systemic AEs is described in section 7.1.1, Solicited Adverse Events.

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.
- AEs leading to withdrawal: adverse events leading to study or vaccine withdrawal.

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If solicited or unsolicited adverse events have been reported and the subject and/or parent(s)/legal guardian(s)] indicated that the symptoms required medical attendance or were of concern, the subject and/or parent(s)/legal guardian(s) must be contacted for further information.

When the subject and/or parent(s)/legal guardian(s) is contacted for any of these reasons, the contact must be documented in the subject's source documentation.

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. The investigator's assessment of ongoing Adverse Events at the time of each subject's last visit should be documented in the subject's medical chart.

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.

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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 studyvaccine. SAEs that are judged to be possibly or probably related to the studyvaccine should be reported to the Sponsor as related events.

The relationship of the studytreatment to an SAE will be determined by the investigator based on the followingdefinitions:

1. Related

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, Evaluation of Adverse Events).

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 studyvaccine to an SAE will be determined by the investigator.

In addition, SAEs willbe evaluated by the Sponsor or designee for "expectedness." An unexpected AE is one that is not listed in the ct11Tent 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 occt11Ted 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 hospitalizationwould 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

Adverse Events of Special Interest (AESis) will not be assessed during the study.

7.1.S Methods for Recording Adverse Events and Se1ious Adverse Events

Findings regarding Adverse Events must be reported on an Adverse Events CRF, as specified in section 7.1.1, Solicited Adverse Events, and on the VSAE form, if applicable,

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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. Specifically, once an investigator becomes aware that a SAE has occurred in a study subject, the investigator (or designate) must complete a paper expedited Adverse Events report and forward it to GSK WITHIN 24 HOURS. The report will always be completed as thoroughly as possible with all available details of the event and then dated and signed by the investigator (or designate). Even if the investigator does not have all information regarding a SAE, the report should still be completed and forwarded to GSK within 24 hours. Once additional relevant information is received, the report should be updated and forwarded to GSK WITHIN 24 HOURS. The investigator will always provide an assessment of causality at the time of the initial report. 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 GSK or its designee will contact the investigator if it is necessary to obtain further information for assessment of the event. Of note, after the initial AE/SAE report, the investigator is required to proactively follow each subject and provide additional relevant information on the subject's condition to GSK Biologicals (within 24 hours for SAEs, and within 2 weeks for pregnancies).

All SAEs must be reported by the investigator to his/her corresponding EC/ IRB 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/IRB and other relevant authorities.

7.1.5.1 Post-Study Events

AnySAEthat occurs outside of the protocol-specifiedfollow-up period and considered to be caused by the study vaccine nrust 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 I month after Last Subject Last Visit (LSLV). Instructions and contact details for collecting and reporting these suspected SAEs will be provided to the investigato.r

7.1.6 Pregnancies

To ensuresubjects' safety, each pregnancy in a subject after study vaccination must be reported to GSK or delegate in due time 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 GSK or delegate. 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, Serious Adverse Events) must also be reported on the VSAE Report Form The following should always be considered as SAE.

- Spontaneous pregnancy loss, including

  spontaneous abortion, (spontaneous pregnancy loss before/at 22 weeks of gestation)

  ectopic and molar pregnancy

  still birth (intrauterine death of foetus after 22 weeks of gestation).

  Note: the 22 weeks cut-off in gestational age is based on WHO-ICD 10 noted in the EMA Guideline on pregnancy exposure. It is recognized that national regulations might be different.

- Any early neonatal death (i.e. death of a live born infant occurring within the first 7 days of life).

- Any congenital anomaly or birth defect (as per the Metropolitan Atlanta Congenital Defects Program (Erro r! Refer ence sour ce not foun d.) guidelines) identified in the offspring of a study subject (either during pregnancy, at birth or later) regardless of

whether the foetus is delivered dead or alive. This includes anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion.

7.1.7 Safety Laboratory Measurements

No safety laboratory measurements will be done in this study.

7.2 Efficacy Assessment

This section is not applicable. This studyhas no efficacy measurements.

7.3 Immunogenicity Assessment

The functional measure of inununogenicity used in this study, Serum Bactericidal Assay (SBA), is a measure of the ability of antibodies, in concert with human complement, to kill meningococci, and is widely used and generally recognized as the serological correlate of protection. The key measures of inununogenicity will be the percentages of subjects with seroresponse,[1] percentages of subjects who achieve hSBA titers 8 and, and the hSBA GMTs against serogroups A, C, W and Y reference strains

These measurements will be assessed in serology samples collected at Visit Day 1, 4 or 6 and Day 29. The measures of inununogenicity used in 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 inunune response).

All subjects will have a blood draw at Day 1, before vaccination. Subsequent blood draws will be at either Day 4 or Day 6 post vaccination, and at Day 29 post vaccination.

Testing will be conducted by qualified and certified laboratories. All assays will be performed in GSK Clinical Laboratory Sciences or delegate laboratory, as provided in the protocol ancillary document.

[1] Seroresponse is defined for this study as follows: Seroresponse to N. meningitidis serogroups A, C, W and Y is defined as: For subjects with pre-vaccination titers <4, post-vaccinatioo titers 2: 16; for subjects with pre-vaccination titers 2:4, post vaccination titers at least 4 times the pre-vaccination titers.

8. STATISTICAL CONSIDERATIONS

8.1 Endpoints

8.1.1 Plimai-y En dpoin t(s)

8.1.1.1 P1im ary Saf ety En dpoin t(s)

There are no primary safety endpoints in this study.

8.1.1.2 P1imar y Efficacy En dpoint (s)

There are no primary efficacy endpoints in this study.

8.1.1.3 P1imar y Immunogenicity E ndpoin t(s)

The following measure willbe summarized for the Menveo-Menveo and Menactra-Menveo groups:

1. Percentage of subjects with hSBA seroresponse[1] against *N. meningitidis* serogroups A, C, W and Y at Day 29.

8.1.2 Secondary Endpoint(s)

8.1.2.1 Secondary Safety Endpoint(s)

Safety of the study vaccine willbe assessed in the Menveo-Menveo, Menactra-Menveo, Naive and the pooled (Menveo-Menveo and Menactra-Menveo) groups in temlSof the frequencies (percentages) of reported adverse events including:

1. Any unsolicited AEs reported within 30 minutes after vaccination;
2. Solicited local and systemic AEs reported from Day 1 (6 hours) through Day 7 after vaccination;
3. Other indicators of reactogenicity (e.g. use of analgesics / antipyretics, body temperature) within 7 days after vaccination;
4. All unsolicited AEs reported from Day 1 through Day 29 after vaccination;

[1] Seroresponse is defined forthisstudy asfollows: For subjectswith pre-vaccinationtiters <4, pos-t vaccination titers 2: 16; for subjects with pre-vaccinationtiters2::4, post vaccination titers at least4 timesthe pre-vaccinationtiters.titers.

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5. Medically-attendedAEs, AEs leading to withdrawal and SAEs reported from Day 1 through Day 181 (entire study period).

Adverse events will be coded using MedDRA preferred terms as applicable.

8.1.2.2 Secondary Efficacy Endpoint(s)

There are no secondary efficacy endpoints in this study.

8.1.2.3 Secondary Immunogenicity Endpoint(s)

The following measures will be summarized for Menveo-Menve,oMenactra-Menveo, Naive and the pooled (Menveo-Menveoand Menactra-Menveo)groups:

1. Percentage of subjects with hSBA titer 8 and 16 against*N. meningitidis* serogroups A, C, Wand Y at Day 1, Day 4, Day 6 and Day 29 and between-group differences;
2. Percentagesof subjects with hSBA seroresponse[1] against *N. meningitidis* serogroups A, C, Wand Y at Day 4, Day 6 and Day 29 and between-group differences;
3. hSBA GMfs againstN. *meningitidis* serogroup A, C, Wand Y at Day 1, Day 4, Day 6 and Day 29;
4. Ratios ofhSBA GMfs atDay 1, Day 4, Day 6 and Day 29 (between study groups).
5. hSBA Geometric Mean Ratios (GMRs) at Day 4, Day6, and Day 29 compared to Day 1 (within study groups).

8.1.3 Explora tory Endpoint(s)

8.1.3.1 Exploratory Safety Endpoint(s)

There are no exploratory safety endpoints in this study.

8.1.3.2 Explor atory Efficacy Endpoint(s)

There are no exploratory efficacy endpoints in this study.

[1] Seroresponse is defined forthisstudy asfollows: For subjectswith pre-vaccinationtiters <4, pos-t vaccination titers 2: 16; forsubjects with pre-vaccinationtiters2::4, post vaccinationtiters at least4 timesthe pre-vaccination titers.

8.1.3.3 Exploratory Immunogenicity Endpoint(s)

There are no exploratory immunogenicity endpoints in this study.

8.2 Success Criteria

8.2.1 Success Criteria for Primary Objective(s)

8.2.1.1 Success Criteria for Primary Safety Objective(s)

There are no primary safety objectives in this study.

8.2.1.2 Success Criteria for Primary Efficacy Objective(s)

There are no primary efficacy objectives in this study.

8.2.1.3 Success Criteria for Primary Immunogenicity Objective(s)

To demonstrate immune response sufficiency after MenACWY-CRM booster vaccine administration, the lower limit of the one-sided 97.5% Confidence Interval(CI) for percentage of subjects with hSBA booster seroresponse against each of serogroups A, C, W and Y must be greater than 75%. This will be tested sequentially first in the group of subjects who received primary vaccination with Menveo and, if met, also in the group of subjects who received primary vaccination with Menactra.

8.2.2 Success Criteria for Secondary Objective(s)

8.2.2.1 Success Criteria for Secondary Safety Objective(s)

There are no success criteria associated with the secondary safety objectives.

8.2.2.2 Success Criteria for Secondary Efficacy Objective(s)

There are no secondary efficacy objectives in this study.

8.2.2.3 Success Criteria for Secondary Immunogenicity Objective(s)

There are no success criteria associated with the secondary immunogenicity objectives in this study.

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

Solicited Safety Set (solicited local and systemic adverse events and other solicited adverse events)

All subjects in the Exposed Set with any solicited adverse event data.

Unsolicited Safety Set (unsolicited adverse events)

All subjects in the Exposed Set with unsolicited adverse event data.

Overall Safety Set

All subjects who are in the Solicited Safety Set and/or Unsolicited SafetySet.

8.3.4 Full Analysis Set (FAS) Efficacy/Immunogenicity Set

Full Analysis Set Immunogenicity

FAS <Day 1)

All subjects in the All Enrolled Set who:

- are randomized;
- provide evaluable serum samples at Day 1 whose result is available for at least one serogroup.

FAS <Day29)

All subjects in the All Enrolled Set who:

- are randomized;
- receive the study vaccination;

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- provide evaluable serum samples at Day 1 whose result is available for at least one serogroup (except for hSBA titer 8 and 16, GMTs and GMRs calculated at specific timepoints);
- provide evaluable serum samples at Day 29 whose result is available for at least one serogroup.

8.3.S Per Protocol (PP) Set Efficacy/Immunogenicity Set

A PPS will be defined for each FAS described in the previous Section with additional criteria specified below.

All subjects in the FAS Immunogenicity who

- Have no protocol deviations leading to exclusion (see section 8.3.8, Protocol Deviation)s as defined prior to unblinding / analysis.
- Are not excluded due to other reasons defmed prior to unblinding or analysis (see section 8.3.8, Protocol Deviations)

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

Subjects who withdrew informed consent.

8.3.6 Other Analysis Sets

There are no other analysis sets used in this study.

8.3.7 Subgroups

Using the PPS (Day 29), the analyses of the primary objectives will be replicated by sex and race.

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. CSR-reportable protocol deviations will be defined as exclusionary from the analysis according to protocol objectives and endpoint,s 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

8.4.1 Analysis of Demographic and Baseline Characteristics

Descriptive statistics (mean, standard deviation, median, minimwn and maximwn) for age, height and weight at enrolment will be calculated overall and by study group.

Distributions of subjects by sex, race and ethnic origin will be summarized overall and by study group.

8.4.2 Analysis of Primary Objective(s)

8.4.2.1 Analysis of Primary Safety Objective(s)

There are no primary safety objectives in this study.

8.4.2.2 Analysis of Primary Efficacy Objective(s)

There are no primary efficacy objectives in this study.

8.4.2.3 Analysis of Primary Immunogenicity Objective(s)

8.4.2.3.1 Statistical Hypotheses

Null hypothesis: $P,j \quad 0.75$

versus

Alternative hypothesis: $Pij > 0.7\ 5$

Where: P,j is the population booster seroresponse rate; j = 1,2 refer to group Menveo-Menveo (first test) and Menactra-Menveo (second test) respectively; i = 1,2,3,4 refer to serogroup A, C, W and Y respectivel.y The level of significance is fixed at one-sided 0.025.

8.4.2.3.2 Analysis Sets

The analysis population to be used for the primary objectives is the PPS (Day 29). Analyses of primary objectives will be repeated on the FAS (Day 29) to assess robustness of results.

8.4.2.3.3 Statistical **Methods**

General

Missing immunogenicityvalues are assumed MCAR (Missing Completely At Random) and therefore may not contain information that impact the result of the analysis (i.e., not informative). Imputation methods will therefore not be used.

Overall significance level for all hypothesis tests is one-sided α = 2.5%.

Seroresponse (Day 29)

Seroresponse for this booster study is defined as: a) post-vaccination hSBA titer ,::16 for subjects with a pre-vaccination hSBA titer <4; b) forsubjects with a pre-vaccination hSBA titer ,::4, an increase of at least four times the pre-vaccinationhSBA titer.

For each individual vaccine group (Menveo-Menveo and Menactra-Menveo) and each ACWY serogroup, the percentage of subjects with seroresponse will be computed, along with associated two-sided 95% Clopper-Pearson Cis.

Further details of the statistical methods will be provided in the SAP.

8.4.3 Analysis of Seconda ry Objective(s)

8.4.3.1 Analysis of Seconda ry Safety Objective(s)

8.4.3.1.1 Analysis of Ext ent of Exposur e

Subjects will be analyzed to the extent that they were exposed to study vaccines and according to the available safety data for the subject during any study period. Subjects who withdraw early or who are lost to follow-up will be removed from the summary table denominator for the time period in which they have no available safety data collected.

8.4.3.1.2 Analysis of Solicited Local,Systemic and Other Adverse Events

All solicited adverse events will be summarized according to defined severity grading scales.

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

Post-vaccinationsolicited adverse events reported from Day 1 to Day 7 will be summarized forthe intervals Day 1 (6 hours) - Day 3, Days 4-7, Day 1 (6 hours) - Day 7 by maximal severity and by study group. Separate analyses will be performed for solicited AEs reported 30 minutes after vaccination. Theseverity of solicited local adverse events, including injection-site erythema and induration, will be categorized based on linear measurement: None (0-24 mm), Mild (2S-SOmm), Moderate (S1-100 mm), Severe (> 100mm).

Injection site pain and systemic reactions, including fatigue, headache, myalgia, arthralgia, chills, nausea, loss of appetite, occurring up to 7 days after each vaccination will be nmmari7ed according to "mild", "moderate" or "severe".

Each solicited local and systemic adverse event will also be further summarized as "none" versus "anY'.

Use of antipyretics and analgesics will be summarized by frequency, by type of use (prophylactic versus treatment) and percentage of subjects reporting use.

Body tefl1lElrature will be summarized separately according to the 3 schemes described below and will be broken down according to route of measurement:

- by O.S °C increments from 36.0°C upto ,::40°C;
- by 1°C increments: <36.0, 36.0-36.9, 37.0-37.9, 38.0-38.9, 39.0-39.9, ,::40°C;
- According to different cut-offs (< versus ,::): 38.0, 38.S, 39.0, 39.S, 40.0°C.

8.4.3.1.3 Anal y sis of U n so licited Advene Events

This analysis applies to all adverse events occurring during the study, judged either as probably related, possibly related, or not related to vaccination bythe investigato,r recorded in AE CRF, with a start date on or after the dateof first vaccination. AE starting prior to the first vaccination willonly 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 systemorgan class (SOC).

All reported adverse events, as well as adverse events judged by theinvestigator as at least possibly related to study vaccine, will be summarized according toSOC and preferred term within SOC. These summaries will be presented bystudy group 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 will be counted.

Separate summaries will be produced for the following categories:

- Adverse events that are possibly or probably related to vaccine
- Unsolicited AEs reported within 30 minutes after vaccination
- Unsolicited AEs reported within 29 days after vaccination
- Adverse events leading to withdrawal
- Adverse events leading to a medically attended visit
- Serious adverse events
-

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.

8.4.3.1.4 Statistical Hypotheses

There are no statistical hypotheses associated withthe secondary safety objectives.

8.4.3.LS Analysis Sets

Analyses of solicited adverse events - and other solicited reactions - and unsolicited adverse events will be performed on the relevant safety sets.

8.4.3.1.6 StatisticalMethods

For unsolicited adverse events, the entirestudy period will be divided into the following intervals: onset within30 minutes after vaccination, onset within 28 days after vaccination; and from Day 1 through Day 181. For solicited adverse events, the solicited study period will be divided into intervals: from 6 hours through day 3; from day 4 through day 7; and from 6 hours through day 7.

No imputation methods willbe used to address missing safety data.

SnmmariP.s of safety will be presented using frequencies and percentages within each study group. No statistical comparisons among the studygroups with respect to any of the safety parameters will be performed.

8.4.3.2 Analysis of Secondary Efficacy Objective(s)

There are no secondary efficacy objectives associated with this study.

8.4.3.3 Analysis of Secondary Immunogenicity Objective(s)

8.4.3.3.1 Statistical Hypotheses

Analyses related to the secondary immunogenicityobjectives willbedescriptiv;eno formal statistical tests will be performed.

8.4.3.3.2 Analysis Sets

Analyses of secondary imm1mogenicity will be based on the PPS and repeated on the FAS.

8.4.3.3.3 Statistical Methods

General

The hSBA titers at each visit will belogarithmicallytransformed (basel 0) to obtain approximately normally distributed data.

For comparison of percentages and GMT ratios, unadjusted estimates will beobtained along with adjusted estimates from regression models to account for potential baseline imbalance between study groups.

For each*N. m.eningitidis* serogroup A, C, Wand Y, unadjustedGMTs will becalculate,d withtheir associated two-sided 95% Cls, by exponentiating the corresponding log-transformed means and their 95% Cls. Adjusted GMTs willbeobtained from Analysis of Covariance (ANCOVA) models.

See section 8.4.2.3.3 for other relevant details.

Seroresponse (Day 4, Day 6, and Day 29)

The percentage of subjects withseroresponse and associated two-sided 95% Clopper-Pearson Cls willbecomputed by group (Menveo-Menveo, Menactra-Menveo, the Nai've and the pooled [Menveo-Menveo and Menactra-Menveo]groups) and*N. m.eningitidis* serogroups A, C, W and Y teststrains. Differences in percentages and associated 95% Cls between study groups willbecalculated using the Miettinen & Nurminen score method.

In a descriptive fashion - using the difference in percentages and 95% Cls - each of the previously vaccinated groups (individually and pooled [Menveo-Menveoand Menactra-Menveo]) will becompared to the nai've group. Also the two previously vaccinated study groups willbecompared to each other.

As sensitivity analyses, the difference in percentages willalso be obtained from a log-linear model adjusting for pre-vaccinationtiter. Please see SAP for technical details.

Percenta ge of Subjects \Vith hSBA titer<!.8 (Da y I, Da y 4, Da y 6, and Da y 29)

F or each study group and in the pooled group (Menveo-Menveo and Menactra-Menveo), the percentage of subjects with hSBA titer 8 and 16 and associated two-sided 95% Clopper-Pearson Cls willbecomputed by the *N. meningitidis* serogroups A, C, W and Y teststrains on Day 1, Day 4, Day 6 and Day 29 (as applicable, depending on blood draw schedule).

Differences in percentages and associated 95% Cis between study groups will be calculated using the Miettinen & Nurminen score method.

In a descriptive fushion - using the difference in percentages and 95% Cis - the previously vaccinated groups (individually and pooled [Menveo-Menveo and Menactra-Menveo]) will becompared to the nai've group. Also the two previously vaccinated groups will be compared to each other.

As sensitivity analyses, the difference in percentages willalso be obtained from a log-linear model adjusting for pre-vaccinationtiter. Please see SAP for technical details.

Between-gr oup Ratios of Gl\1T s (A d jus te d a nd Un ad ju sted)

The between -group ratio ofhSBA GMTs and corresponding 95% CI, at each of Visit Day 1 (Persistence), Day 4, Day 6 and Day 29 against each *N. meningitidis* serogroups A, C, W and Y test strains willbeobtained by exponentiatingthe mean between-group differences in log-transformed titers and the corresponding 95% Cls at each of the timepoints specified.

Additionally, adjusted ratio of GMTs willbeobtained fromANCOVA models including pre-vaccination titer as fuctors in the model.

The previously vaccinated groups (individually and pooled [Menveo-Menveoand Menactra-Menveo])willbecompared to the nai've group at each timepoint - descriptively - using the ratios of GMTs.

The two previously vaccinated groups willbecompared at each timepoint using GMT ratios.

\Vit hin-gro up GMRs (Adjusted and Unadjusted)

Within each study group and for each serogroup, GMRs will be calculated, as applicable, at:

- Visit Day4 versus at Visit Day 1;
- Visit Day 6 versus at Visit Day 1; and
- Visit Day 29 versus at Visit Day 1.

The unadjusted GMR.s and 95% Cis willbeconstructed by exponentiating the mean within-groupdifferences in log-transformed titers and the corresponding 95% Cis.

Further details of the statistical methods willbeprovided in the Statistical Analysis Plan (SAP).

8.4.4 Analysis of Explora tory Objectives

8.4.4.1 Analysis of E xplora tory Safety O bjective(s)

There are no exploratory safety objectives in this study.

8.4.4.2 Analysis of Explora tory Efficacy Objective(s)

There are no exploratory efficacy objectives in this study.

8.4.4.3 Analysis of Explora tory Immunogeoicity Objective(s)

There are no exploratory immunogenicityobjectives in this study.

8.5 Sample Size and Power Considera tions of Primary and Secondary Objectives

Statistical power was estimated based on observed data from a previous study (V59Pl3 El) assessing the immunogenicityof a booster dose ofMenveo among subjects who had previously been vaccinated with either Menveo or Menactra 3 years prior in another study (V59P13) whilesubjects were 11-18 years old. Data from study V59Pl3 E1, were used to compute booster seroresponse rates at one-monthpost booster dose of MenACWY-CRM using the following definition of booster seroresponse: a) post-vaccination hSBA titer,:: 16 for subjects with a pre-vaccinationhSBA titer <4; b) for subjects with a pre-vaccination hSBA titer ,::4, an increase of at least four times the pre-vaccination hSBA titer (cf. table 8.5-1).

Table 8.5-1: hSBASeroresponse at One Month Following the Booster at 3 Years After Vaccination, bySerogroup - Booster- PP Population

	Vaccination	ACWY/A Y Group IV	l\fenactr a/ACWY Gt·onp V
<l'.	Overall Seroresponse	68(97%) (90-100) N=70	70 (100%) (95-100) N=70
u	Overall Seroresponse	66(93%) (84-98) N=71	*65* (93%) (84-98) N=70
	Overall Seroresponse	63 (91%) (82-97) N=69	64 (93%) (84-98) N=69
>	Overall Seroresponse	63 (90%) (80-96) N=70	64 (91%) (82-97) N=70

Assuming the true booster seroresponse rates in the Menveo-Menveogroup range from 90% to 97% (alternative hypothesis) for each serotype, a sample sizeof n=270will have at least 96% power to show sufficiency of immune response to a booster dose of MenACWY-CRM, compared with a pre-specifiedreference booster seroresponse of7S% (null hypothesis) using an exact test with 0.02Sone-sidedsignificance level (cf table 8.S-2a).

Assuming the true booster seroresponse rates in the Menactra-Menveogroup range from 91% to 100% (alternative hypothesis) for each serotype, a sample sizeof n=270will have at least 96% power to show sufficiency of immune response to a booster dose of

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MenACWY-CRM, compared with a pre-specified reference booster seroresponse of 75% (null hypothesis) using an exact test with 0.02Sone-sided significance level (cf table 8.S-2b).

Table 8.S-2a: Statistical Power to Test for Sufficiency of Immune Response Given a Range of True Booster Seroresponse Rates for Evaluable Sample Size of 270 subjects in the Menveo-Menveo group

Serot}11e	T111eSeroresponse Rate	Power
A	0.97	0.99
C	0.93	0.99
W	0.91	0.99
y	0.90	0.99
Total Power		0.96

Calculations havebeendone with nQuety Advisor (Version 7.0).

Table 8.S-2b: Statistical Power to Test for Sufficiency of Immune Response Given a Range of True BoosterSeroresponse Rates for Evaluable Sample Size of 270 subjectsin the Menactra-1\lle n veo gro u p

Se.-0!}11e	T111e Seroresponse Rate	Power
A	>0.99	0.99
C	0.93	0.99
W	0.93	0.99
y	0.91	0.99
Total Power		0.96

Calculations havebeendone with nQuety Advisor (Version 7.0).

Overall statistical power to show sufficiency of immune response to a booster dose of MenACWY-CRM for each serotype in both the Menveo-Menveo and the Menactra-Menveo group will be at least 92%.

When taking a 10% dropout rate into account, N=300 previously vaccinated subjects with Menveo and N=300 previously vaccinated subjects with Menactra have to be enrolled in the study.

A total of 100 meningococcal vaccine-naive subjects are planned to be enrolled in the study for comparisonof immune responses after a single dose in unprimed subjects with the booster response in primed subjects. The sample size of 100 naive subjects is based on

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previous MenACWY studies Pxamining the response to a booster and to ensure a rniuirnnm sample sizeof SOsubjects in each blood draw schedule for adequate compansons.

8.6 Interim Analysis

No interim analysis of data from this studyis planned.

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9. SOURCE DOCUMENTATION, STUDY MONITORING AND AUDITING

In order to ensure consistency across sites, study monitoring and auditing willbe 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 willtrain investigators and/or their study staff on the study protoco allapplicable studyprocedures, documentation practices and all electronic systems. CRFs supplied by the Sponsor must be completed for each randomized subject (see section 8.3.1, All Enrolled Set 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 willbechecked 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 willberequired for review as source documents. The kinds of documents that willserve as source documents willbe agreed between Sponsor or delegate and investigator and designees and specified in the SDAF 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/or parent(s)/legal guardian(s) and date of completion and reason.

The subject and/or parent(s)/legal guardian(s) must also allow access to the subject's medical records. Each subject and/or the parent(s)/legal guardian(s) 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 safetydata 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, thesesources 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 infonnation were used to detennine the adverse event (e.g., subject recall, medical chart, Subject Diary).

9.2 Study Monitoring, Auditing and Sow·ce Data Verification

Prior to enrolment of the first study subject, GSK or its designee (e.g., a CRO) will develop a Clinical 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 byGSK or its designee as frequently as necessary to ensure:

- that the rights and well-beingof 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 cUITent approved protocol/amedlment(s), GCP and applicable regulatory requirements.

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

Data verification may also be performed through a centralized review of data (e.g., checking for outliers or other anomalies). Additional documents such as the investigator site file, pharmacy records, and infonned 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 byGSK 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 regulation,sbyofficials 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 confidentialitylaws for use and disclosure of infonnation related to the study and enrolled subjects.

10. DATAMANAGEME1''T

10.1 Data Enh·y and Management

In this study, all clinical data (including, but not limited to, *AEISAEs,* concomitant medications, medical history, and physical assessments), safety data, and immllllogenicity data will be entered onto case report fonns (CRFs) in a timely fashion by the investigator and/or the investigator 's dedicated site staff. Data entered onto CRFs are stored on a secure website. The data collected on this secure website are assimilated into an electronic data capture (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 nrust review data entered and electronicallysign the CRFs to verify their accuracy.

Access to the EDC system for data entryor 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.

10.2 Data Cla1ifi cati on

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, tlJe reason for the change, as well as the time of tlJe 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 willensure the confidentiality of their medical information in accordance with all applicablelaws and regulations.

11. RECORD RETENTION

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records nrust be easily accessible, when needed (e.g. audit or inspection,)and must be available for review in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g. microfiche, scanned, electronic); howeve,rcaution needs to be exercised before such action is taken. The investigator nrust ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generatinga hard copy, if required. Furthermore, the investigator must ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for making these reproduction.s

GSK will inform theinvestigato/rinstitutionof the time period fur retaining these records to comply with all applicable regulatory requirements. Thi,, minimmn retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP, any institutional requirements, applicable laws or regulations, or GSK standards/procedures, otherwise, the minimum retention period will default to 25 years after completion of the study report.

The investigator/institutionnrust notify GSK of any changes in the archival arrangements, including, but not limited to archival at an off-site facility, transfer of ownership of the records in the event the investigator leavesthe site.

The principles for the storage of laboratory samples are provided below:

Collected samples will be stored for a maximum of 20 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK.

12. USE OF JIl,'FORMATION 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 cUITent 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 theend of study as defined in section 3.9, End of Study.

In accordance withstandard editorial, ethical practices and cUITent guidelines of Good Publication Practice (Graf 2009), GSK will generally support publication ofmulticenter studies only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement prior to the start of the study. The coordinating investigator will also sign the clinical study report on behalf of the principal investigators (CPMP/EWP/2747/00). Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any fonnal publication of the studyin which contribution ofGSK personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate GSK personnel.

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. ETIDCAL CONSIDERATIONS

13.1 Regulatory and Ethical Compliance

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

This clinical study was designed and shall be implemented and reported in accordance withthe ICH Harmonized Tripartite Guidelines for GoodClinical Practice, with applicable local regulations including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry ofHealth, Labor, and Welfare, 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 be included in the study only after providing writteninformed consent or assent, as described in section 5.1.1, Informed Consent/Assent. Before the start of the study, the investigatorwill have the informed consent and any other materials that will be provided to the subjects reviewed and approved bythe IRB/EC. *This* review and approval will be documented and stored with other studydocuments. The investigator or designee must fully inform thesubject 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 thedetails 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 studybefore anystudy-related procedures are conducted. The informed consent process may be conducted up to 5 days prior to vaccination on Day 1. If the subject and/or legal guardian(s) 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 nrust be agreed to byGSK before submission to the IRB/EC and a copy of the approved version must be provided to the GSK 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 doubts on the ability of a subject to adhere to these requirements, that subject should not be allowed in the study

Before the start of the study, the investigator will have the informed assent, the informed consent, and any other materials that will be provided to the subject and/or parent(s)/legal guardian(s) 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 and/or parent(s)/legalguardian(s) of all pertinent aspects of the study. A copy of the written informed consent and informed assent will be given to the subject and/or parent(s)/legal guardian(s).

In addition, the investigator or designee should explain pertinent aspects of the study in an age appropriate manner to pediatric subjects who are eligible for informed assent in accordance with local policies. The subject and parent(s)/legal guardian(s) 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 parent(s)/legal guardian(s) must sign the consent/assent forms indicating their agreement to participate in the study before any study-related procedures are conducted. If the subject and/or parent(s)/legal guardian(s) are unable to read and write, a witness must be present during the informed consent/assentdiscussion and at the time of informed consent/assentsignature.

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 (RI), 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 studystart and at any time the protocol is amended during studyconduct, the investigator is required to sign a protocolsignature page confirming his/her agreement to conduct the study in accordance withthese 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 protoco 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 and/or parent(s)/legal guardian(s) 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 nwnber(s)). In addition, the investigato,ror person designated by the investigato,rshould 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 protocolwhich 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, studyprocedures, or significant administrative aspects. An administrative change of a studyprotocol is a minor correction or clarification that has no significant impact on the waythe clinical study is to be conducted

andnoeffectonsubjectsafety(e.g.,changeoftelephonenumber(s),logisticalchanges). Protocolamendments nrustbeapprovedbyGSK,healthauthoritieswhererequired,and theIRB/EC.In caseswhentheamendmentisrequiredinordertoprotectthesubject safety,theamendmentcanbeimplementedpriortoIRB/ECapproval.Notwithstanding, theneedforformalapprovalofaprotocolamendmen,ttheinvestigatorisexpectedtotake anyinunediateactionrequiredforthesafetyofanysubjectincludedinthisstudy,evenif thisactionrepresentsadeviationfromtheprotocol.In suchcases,GSKshouldbenotified of this action, the IRB/EC at the study site, and, if required bylocal regulations, the relevant health authority) should be informed within 10 working days.

14. REFERENCE LIST

Code of Federal Regulations (1997): Food and Drug Administration, U.S. Depar1ment of Health and Human Services: Title 21, Part 11: Electronic Records Electronic Signatures. Federal Register 62: 13464

European Medicines Agency (2005): EMEA/CHMP/313666/2005 Guideline on the exposure to medicinal products during pregnancy: need for post-authorisationdata, London, 14 November 2005

European Parliament (1995): Directive 95/46/EC of the European Parliament and of the Council of 4 April 2001. Official Journal of the European Communities. L 281/31-39

European Parliament (2001): Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001. Official Journal of the European Communities. L 121/34-44

Graf C, Battisti WP, Bridges D (2009). Good publication practice for communicating company Sponsored medical research: the GPP2 guidelines. BMJ; 339: b4330

ICH (1997) ICH Harmonised Tripartite ICH Guideline for Good Clinical Practices E6 (RI). Federal Register, 62 (90): 25691-25709

ICH (1998) ICH Harmonised Tripartite ICH Guideline for Statistical Principles for Clinical Trials E9. Federal Register, 63 (179): 49583

Levine RJ. (1988) Ethics and Regulations of Clinical Research. New Haven: Yale University Press.

Metropolitan Atlanta Congenital Defects Program (MACDP)
http://www.cdc.gov/ncbddd/birthdefects/documents/macdpcode0807.pdf

U.S. Depar1ment of Health and Human Services, Food and Drug Administration, CBER (2009): Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

59th World Medical Association General Assembly (October 2008) Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Seoul, Korea

Appendix 1: In vestiga tor Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrativechanges, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline (GSK) Biologicals.
- To assume responsibilityfor the proper conduct of the study at this site.
- That I am aware of, and willcomply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals' study vaccine(s)/product(s) and other study-related duties and functions as described in the protocol.
- To acquire the reference ranges for laboratory tests perfonned locally and, if required by local regulations, obtain the laboratory's cUITent certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serumsamples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally acceptable representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigationalvaccine(s)/product(s), and more generally about his/her financial tieswith the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study.

- Agree that GSK Biologicals may disclose any infonnation it has about such ownership interests and financial ties to regulatory authoritie.s
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

eTrack study number and Abbreviated Title	*205352 (MENACWY CONJ-038 (V59_77))*
IND number:	*IND11278*
Date of protoco:l	
Detailed Title:	*A Phase 3b, Controlled, Open-Label, Multi-Center Study to Evaluate Safety and Immunogenicity of a Single Dose of GlaxoSmithKline's Meningococcal ACWY Conjugate Vaccine (Menveo), Administered to Healthy Individuals 15 through 55 years of age, approximately 4-6 years after primary ACWY vaccination.*
Investigator name:	_____
Signature:	_____
Date:	_____

Novartis

Document A !J!roval Ce rtificate /

PPD

PP - - -' /

The indivi:luals listed have appl'()ved this document for ii!Jplementation using an electronic signature in the Atlas EDMS. tFPO

U serName:pp-o• - - - .. PP D

Ti tle: Cluster Phys ician -Meningi t is an d Sepsis Franchise

Date: Friday, 12 August 20 16 , 12 :44 GMT

Meaning: As an approver, I agree with the content and format of this document

ai

CLINICAL STUDY PROTOCOL VS9 77 **Version** 2

A Phase 3b, Controlled, Open-Label, Multi-Center Study to Evaluate Safety and Inumnogenicity of a Single Dose of GlaxoSmithKline's Meningococcal ACWY Conjugate Vaccine (Menveo), Administered to Healthy Individuals 15 through 55 years of age, approximately 4-6 years after primary ACWY vaccination.

Safety and Immunogenicity Study of a Single Dose of Menveo, Administered to Subjects 15 through 55 years of age, approximately 4-6 years after primary ACWY vaccination

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Name of Sponsor:	**Protocol number:**	**Gene1ic name of study vaccine(s):**
GlaxoSmithKline Vaccines	V59 77	Meningococcal (groups **A,** C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine

Titl e of Study: A Phase3b, Controlled, Open-Label,Multi-Center Study to Evaluate Safety and Immunogenicity of a Single Dose of GlaxoSmihKline's Meningococcal ACWY Conjugate Vaccine (Menveo,)Administered to HealthyIndividuals 15 througll *55* years of age, approximately 4-6 years after primary ACWY vaccination.

Study **Pe1iod:** Approximately 180 days (six months).	**Clinical Phase:** 3b

Background and Rationale:

Neisseria meningitidis is a leadingcause of bacterial meningitis and sepsis worldwide, capable of causing outbreaks and epidemics of invasive disease. Meningococcal disease is associated with higll morbidity and mortality even among patients who receive early antibiotictreatment. Most cases of invasive disease worldwide are caused byserogroups A, B, C, W and Y.

The quadrivalent meningococcal oligosaccharidediphtheria CRM-197 conjugate vaccine (MenACWY-CRM; Menveo, GSK Vaccines) is approved for active immunization of individuals from 2 months througll *55* years of age in the United States. As of February 2015, more than 30,000of subjects have been exposed to MenACWY-CRM vaccine in completed clinical studies and more than 24million doses of the vaccine have been distributed globally

The US Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination with a quadrivalentconjugated meningococcal vaccine for adolescents at 11-12 years of age with a booster dose administered *5* years later. While a substantial body of data exists showing a robust immune response and good antibody persistence after a single dose of MenACWY-CRM in adolescents, the response to a booster dose of MenACWY-CRM in this agegroup has only been evaluated in 2 clinical studies with limited number of subjects.

A robust anamoestic immune response to a booster doseofMenveo vaccine administered at approximately *5* years after previous vaccination with the same vaccine or a licensed meningococcal oolysaccharide vaccine (Menomune®) was demonstrated in

Name of Sponsor:	Protocol number:	Gene1i c name of study vaccine(s):
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the phase 2 clinical study V59P6El . High titers of bactericidal antibodies against the vaccine serogroups were achieved at 7 and 30 days after booster dose in MenACWY-primed subjects. However, the number of subjects included in this studywas relatively small (N=l 0l , including 50 subjects who received a booster dose after the primary MenACWY-CRM vaccination).

In the phase 3b clinical study V59Pl3 El , a booster dose of MenACWY-CRM was given 3 years after primary vaccination with either MenACWY-CRM or Menactra®(a meningococcal diphtheria toxoid-conjugated MenACWY vaccine, MenACWY-D) in adolescents. A booster dose was able to substantially increase antibody titers against all 4 serogroups irrespective of the priming vaccine. Again, only a small number of subjects (N=160) received the MenACWY-CRM booster, (83 who received primary MenACWY-CRM and 77 who received MenACWY-D).

In the light of the current ACIP recommendation for a booster dose of MenACWY-CRM, there exists a need to evaluate the response to a MenACWY-CRM booster given at -5 years after primary vaccination in meningococcaŀvaccine primed adolescents. Generation of this data would also be of relevance in outbreak management and vaccination of travelers to endemic areas.

The purpose/aim of this study is to assess the safety and antibodyresponse to vaccination with a booster dose of Menveo given 4-6 years afterprimary vaccination and the response to a singledose given to vaccine-naive subjects, and to describe the inlmune response over time after a single dose of Menveo, administered to subjects previously vaccinated with Menveo or Menactra or to vaccine-naive subjects. The inclusion of vaccine-naive subjects in a separate study arm is to enable comparison of the rapidity and magnitude of an aoarooestic response to a booster dose (in primed individuals) or the primary response to a first dose (in naive individuals) of MenACWY-CRM.

Study Objectives:

Pli ma ry Objective(s): Immunogenicity objective:

L To demonstrate a sufficient inlmune response following a single dose of MenACWY-CRM(Menveo) vaccine, !rivento subjectswhopreviouslyreceived

Name of Sponsor:	Protocol number:	Gene1i c name of study vaccine(s):
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Menveo or Menactra, as measured by the percentage of subjects with hSBA seroresponse against*N. meningitidis* serogroups A, C, W and Y at Day 29 after vaccination

*Criteria to demonstrate immune response sufficiency: The immune response will be considered as sufficient if the lower limit of the one-sided 97.5% CI for percentage of subjects with hSBA seroresponse against serogroups **A, C,** W and Y is greater than 80% (in pooled group of subjects who received primary vaccination with Menveo or Menactra).*

Seco ndary O bjec tive(s) :

Immunogenicity objectives:

1. To compare the immunogenicityofa single dose ofMenACWY-CRM vaccine, between subjects who previously received Menveo, subjects who previously received Menactra and vaccine-naive individuals, as measured by the percentage of subjects with hSBA titer 8, withhSBA seroresponse, and hSBA GMTs against*N. meningitidis* serogroups A, C, W and Y at Day 29 after vaccination
2. To compare the immune responses following a single dose ofMenACWY-CRM vaccine, between subjects who previously received Menveo, subjects who previously received Menactra and vaccine-naive individuals, as measured by the percentage of subjects with hSBA titer ,::8 and hSBA GMTs against*N. meningitidis* serogroups A, C, W and Y at Day I, Day 4, Day 6, and Day 29 after vaccination
3. To assess persistence of bactericidal antibodies against serogroups A, C, W and Y at approximately 4-6 years after the primary vaccination with Menveo and after the primary vaccination with Menactra in comparison with naturally-acquiredlevel in vaccine-naive individuals, as measured by the percentage of subjects with hSBA titer ,::8 and hSBA GMTs at Day 1.
4. To compare the immune response to a single dose ofMenACWY-CRM vaccine, between subjects who previously received Menveo, subjects who previously received Menactra and vaccine-naive individuals, by age group (15-25 and 26 years of age), as measured by percentages of subjects with hSBA titer ,::8, hSBA seroresponse and hSBA GMTs at Day 29.

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
GlaxoSmithKline Vaccines	V59 77	Meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine

Safety objectives:

1. To assess reactogenicity and safety of MenACWY-CRM vaccine when administered to subjects who previously received Menveo or Menactra and vaccine-naive individuals

Study Design:

This is a phase 3b, controlled, open-label, multi-center study to evaluate safety and immunogenicity of MenACWY-CRM after a single vaccination in healthy individuals who were vaccinated with Menveo or Menactra 4 to 6 years ago and in vaccine-naive individuals.

Study population: Approximately 700 healthy subjects 15 through 55 years of age will be enrolled in the study.

Duration of the study: The duration of this study is approximately 6 months per subject.

Written informed consent and, as applicable according to local guidelines, written assent will be obtained before conducting any study-specific procedures.

Vaccination schedule: All subjects will receive a single dose of MenACWY-CRM at Day 1.

Study groups:

- Group Menveo-Menveo: approximately 300 subjects, who were vaccinated with a single dose of Menveo 4 to 6 years ago, will receive one dose of MenACWY-CRM.
- Group Menactra-Menveo: approximately 300 subjects, who were vaccinated with a single dose of Menactra 4 to 6 years ago, will receive one dose of MenACWY-CRM.
- Group Naive: approximately 100 subjects, of similar age to subjects enrolled in other primed groups, equally enrolled across all clinical sites, who have not received any meningococcal vaccination, will receive one dose of MenACWY-CRM.

Randomization/ Stratification:

Name of Sponsor:	**Protocol number:**	**Gene1i c name of study vaccine(s):**
GlaxoSmithKline Vaccines	V59 77	Meningococcal (groups **A,** C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine

Within eachstudy group, subjects will be enrolled across age range of 15 to *55* years of age as follows:

- Menveo-Menveo and Menactra-Menveo groups: approximately 80% of subjects will be enrolled in age group of 15 to 25 years and 20% of subjects willbe enrolled in 26-55 years age group;
- Naive group approximately 50% of subjects will be enrolled in age group of 15 to 25 years and 50% of subjects willbe enrolled in age group of26-55 years.

Within each age category in each studygroup, subjects willbe randomized into one of two different blood draw schedules according to a 1:1 ratio, described as follows:

- Subjects getting blood draws at Day 1, Day 4 and Day 29.
- Subjects getting blood draws at Day 1, Day 6 and Day 29.

For a schematic overview, see Table 1.

Ta ble I: Schema tic diagra m of the VS9_77 stu dy gro ups

Vacdne History	Vacdnation in c un ent study	**Age Category**	**Blood draw**schednle
Menveo N=300	Menveo	15-25 years (N=240)	Blood draw Day I, 4, 29 (N=l 20)
			Blood draw Day I, 6, 29 (N= l20)
		26-55 years (N=60)	Blood draw Day 1, 4, 29 (N=30)
			Blood draw Day I, 6, 29 (N=30)
Menactra N=300	Menveo	15-25 years (N=240)	Blood draw Day I, 4, 29 (N=l 20)
			Blood draw Day I, 6, 29 (N= l20)
		26-55 years (N=60)	Blood draw Day 1, 4, 29 (N=30)
			Blood draw Day I, 6, 29 (N=30)
Vaccine-Naive N=lOO	Menveo	15-25 years (N=50)	Blood draw Day 1, 4, 29 (N=25)
			Blood draw Day I, 6, 29 (N=25)
		26-55 years (N=50)	Blood draw Day 1, 4, 29 (N=25)
			Blood draw Day I, 6, 29 (N=25)

Blinding: open-label study.

Name of Sponsor:	Protocol number:	Gene1i c name of study vaccine(s):
GlaxoSmithKline Vaccines	V59 77	Meningococcal (groups **A,** C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine

Blood samn!P.s: Three (3) blood samples of approximately 10 mL each will be collected according to the blood draw schedule in Table I.

Data collection: Electronic Case Reporting Form (eCRF).

Study clinic visits: Three (3) clinic visits at Day 1, Day 4 or Day 6 and Day 29 are planned for each subject.

Reminder Phone calls: Two (2) reminder phone calls will beconducted at Day 3 and Day *5* after the study vaccination to remind the subject/ legal guardian to complete the diary card.

Safety phone calls: Three (3) safety phone calls (at Day 15, Day91 and Day181) will be conducted to collect any medically-attended AEs, AEs leading to withdrawal, SAEs, related medications and any vaccinations. In addition, all unsolicited AEs and related medications occurring after the vaccination will be collected during the safety call at Day15. The Day 181 Safety Phone call will also serve as the termination visit.

Solicited Adverse Events (injection site pain, erythema, induration, fatigue, headache, myalgia, arthralgia, loss of appetite, nausea, chills and fever) occurring on the day of vaccination and the following six days (Day I through Day 7) will be recorded daily using a Diary Card for all subjects.

Unsolicited AEs occurring within 28 days after studyvaccination will be collected. Qualified site staff will interview the subject by phone approximately 14 days after vaccination and in person at the studysite approximately 28 days after study vaccination to assess the occurrence of any unsolicited AEs.

Medically-attended AEs AEs leading to studywithdrawal and SAEs will be collected during the entire study period. These data will be captured by interviewing the subject and/or subjects' parents/ guardian (as applicable) during the site visits and phone calls and by review of available medical records. Subjects and/or parents/ guardian will be encouraged to call the site in theevent of any medically-attendedAEs or any AEs which theyperceive as being of concern during the entire studyperiod.

Name of Sponsor:	Protocol number	Generic name of study vaccine(s):
GlaxoSmithKline Vaccines	V59_77	Meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine

Table 2: Schematic diagram of the V59_77 study design.

Day 1	Day 4	Day 6	Day 15	Day 29	Day 91	Day 181
Blood draw (all subjects) Menveo	Blood draw (50%)	Blood draw (50%)	Safety Phone call	Blood draw (all subjects)	Safety Phone call	Safety Phone call Study termination

Number of Subjects planned: Approximately 700 subjects are planned for enrollment into this study, approximately 300 subjects who previously received Menveo (Menveo-Menveo group), 300 subjects who previously received Menactra (Menactra-Menveo group) and 100 meningococcal vaccine-naive subjects (Naive group). Assuming a 10% drop-out rate that should provide approximately 630 evaluable subjects.

Study Population and Subject Characteristics: The list of inclusion and exclusion criteria is included in protocol section 4, Selection of Study Population.

Study Procedures: The study includes three clinic visits, one vaccination, three blood draws, and three safety phone calls for each subject. All study procedures associated with the pre-vaccination, vaccination, post-vaccination, unscheduled and study termination visit are described in section 5.0.

Study Vaccines:

GlaxoSmithKline Meningococcal MenACWY-CRM Vaccine (Menveo): Meningococcal (groups A, C, W and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine is supplied as a vial containing 10 µg of serogroup A oligosaccharides and 5 µg of serogroups C, W and Y oligosaccharides, conjugated to *Corynebacterium diphtheriae* CRM197 protein. Overall injection volume of 0.5 mL.

The vaccine will be administered intramuscularly, preferably in the deltoid area of the non-dominant arm

Primary Endpoint(s):

Name of Sponsor:	Protocol number:	Gene1i c name of study vaccine(s):
GlaxoSmithKline Vaccines	V59 77	Meningococcal (groups **A,** C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine

Immunogenicity Endpoints:

The following measures will be summarized for the pooled (Menveo-Menveo and Menactra-Menveo) group.

2. Percentage of subjects with hSBA seroresponse[1] against *N. meningitidis* serogroups A, C, W and Y at Day 29.

Secondary Endpoints:

Immunogenicity endpoints:

The following measures will be summarized for Menveo-Menveo, Menactra-Menveo, Naive and the pooled (Menveo-Menveo and Menactra-Menveo) groups unless otherwise noted:

1. Percentage of subjects with hSBA titer 8 against *N. meningitidis* serogroups A, C, W and Y at Day 1, Day 4, Day 6 and Day 29;
2. Percentages of subjects with hSBA seroresponse against *N. meningitidis* serogroups A, C, W and Y at Day 4, Day 6 and Day 29 (Day 29: Except the pooled group);
3. hSBA GMfs against *N. meningitidis* serogroup A, C, W and Y at Day 1, Day 4, Day 6 and Day 29;
4. Ratios of hSBA GMTs at Day 1, Day 4, Day 6 and Day 29 (between study groups).
5. Ratios of hSBA GMfs at Day 4, Day 6, and Day 29 compared to Day 1 (within study groups).

Safety endpoints:

Safety of the study vaccine will be assessed in the pooled vaccine group (Menveo-Menveo and Menactra-Menveo) and the vaccine-naive group in terms of the frem1encv

[1] Seroresponse is defined as: a) post-vaccination hSBA 8 for subjects with a pre-vaccination hSBA <4; b) for subjects with a pre-vaccination hSBA - an increase of at least four times the pre-vaccination hSBA.

Name of Sponsor:	Protocol number:	Gene1i c name of study vaccine(s):
GlaxoSmithKline Vaccines	V59 77	Meningococcal (groups **A,** C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine

(percentage) of reported adverse events including:

1. Any unsolicited AEs reported within 30 minutes after vaccination;
2. Solicited local and systemic AEs reported from Day 1 (6 hours) through Day 7 after vaccination;
3. Other indicators of reactogenicity (e.g. use of analgesics / antipyretics, body temperature) within 7 days after vaccination;
4. All unsolicited AEs reported from Day 1 through Day 29 after vaccination;
5. Medically-attended AEs, AEs leading to withdrawal and SAEs reported from Day 1 through Day 181 (during the entire studyperiod).

Statistical Analyses:

P1i mary Immunogenicity Objective

The primary population for the analysis of sufficient immune response is the Full Analysis Set (FAS), and will consist of pooled data from the Menveo-Menveoand Menactra-Menveo group (n=540 evaluable).

To demonstrate immune response sufficiency after MenACWY-CRM booster vaccine administration, the lower limit of the one-sided 97.5% Confidence Interval (CI) for percentage of subjects with hSBA seroresponse against each of serogroups A, C, W and Y must be greater than 80% (in the pooled group of subjects who received primary vaccination with Menveo or Menactra)

Hypothesis:

Null hypothesis	Alternative hypothesis
$P_i \leq 0.80$	$P_i > 0.80$

Where: P_i is the population seroresponse rate for the pooled Menveo-Menveo and Menactra-Menveo group; i = 1,2,3,4 refer to serotypes A, C, W and Y respectively.

Sample Size:

Statistical nower was estimated based on observed data from study V59P13El, where

Name of Sponsor:	Protocol number:	Gene1ic name of study vaccine(s):
GlaxoSmithKline Vaccines	V59_ 77	Meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine

seroresponse rates at one-month post booster dose of MenACWY-CRM ranged from: 97% (90%-100%)to 100% (95%-100%) for serogroupA; 93% (85%-98%)for serogroup C; 91% (82%-97%)to 93% (84%-98%) forserogroup W; and 90% (80%-96%) to 93% (84%-98%) forserogroup Y among subjects primed with MenACWY-CRM or Menactra in the three years preceding the study.

Assuming the true seroresponse rates in the pooled group range from 90% to 97% (alternative hypothesis) for each serotype, a sample size of n=540 will have at least 96% power to show sufficiency of immune response to a booster dose of MenACWY-CRM in the pooled group, compared with a pre-specifiedreference seroresponse of 80% (null hypothesis) using anexact test with 0.025 one-sidedsignificance level When taking a 10% dropout rate into account, N=600 previously vaccinated subjects have to be enrolled in the study. Calculations have been done with nQuery Advisor (Version 7.0).

Table 3: **Statistical Power to Test for Sufficiency of Immun e Response Given a Range of True Seroreponse Rates for Evaluable** Sample Size of 540 subjects

Se.-oty pe	T111e Serores po nse Rate	**Powel'**
A	0.97	0.99
C	0.93	0.99
W	0.91	0.99
y	0.90	0.99
Total Power		0.96

In terim Analysis: No interinlanalysis is planned for this study.

Data Monito1ing Committee: No DMC will be utilized for the study.

Table 4 Time and Events Table

	Visit Type	Clinic Visit	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Phone Call
	Study period	Screening	Treatment	Tre.itment	Treatment	Treatment	Treatment	Follow-up	Followup
	Study Day		1	3, 5	4/6•	15	29	91	181
	Visit Window (Days)	-5 to 1	0	2 days (-1/+1), 4 da ys (0/+2) after vacc	3/5 days (-1/+l) after vacc	14 days (-2/+2) after vacc	28days (-7/+14) after Yacc	90days (-14/+14) **aftel' vacc**	180 days (-14/+14) after vacc
	Visit Number	Pre-**vacc.ination**	1	N/A	2	3	4	5	*6*
Study Event	References								
Study Treatment									
Vaccination (vacc)	Section 5.2		X						
Screening and Safety									
Informed Consent"	Section 5.1.1	X							
Medical History	Section *5*.1.2	X							
Physical Exam	Sections *5*.1.2 and 5 .3.1	X	X<		X		X		
Pregnancy Test	Sections 3.5 and 5 .1.2	X	X<						
Exclusion/Inclusion Criteria	Section4	X							
Randomization	Section 5.1.4		X<						
30 Minutes Post InjectionAssessment	Section *5*.2.1		X						

	Visit Type	Clinic Visit	Clinic Visit	**PhoneCall**	Clinic Visit	**Phone Call**	Clinic **Visit**	**Phone** Call	**PhoneCall**
	Study **period**	**Screening**	**Treatment**	**Tre.itment**	**Treatment**	**Treatment**	**Treatment**	**Followup**	**Followup**
	Study Day		**1**	3, 5	**4/6**	**15**	29	**91**	**181**
	Visit Window **(Days)**	-5 to **1**	0	2 days (-1/+l), 4 days(0/+2) **after vacc**	3/5 da)'S (-1/+l) **after** vacc	**14** days (-2/+2) **after vacc**	**28days** (-7/+14) **after Yacc**	90days (-14/+14) **aftel' vacc**	**180** days **(-14/+14) after vacc**
	Visit **Number**	**Pre-vacc.ination**	**1**	**NIA**	2	3	**4**	5	***6***
Study Event	References								
Subject Diary Dispensed with Training	Section 5.2.1		**X**						
Subject Diary Reminder Call	Section 5.2.2			*xi*	*xi*				
Subject Diary Reviewed and Collected	Section 5.3.1						X		
Assess Unsolicited AEs	Section 7.1		**X**		**X**	**X**	X		
Assess SAEs	Section 7.1.4		**X**		**X**	**X**	X	X	X
Assess for medically attended AEs and AEs leading to withdrawal	Sections 7.I.4.I and7.1.3		**X**		**X**	**X**	X	X	X
Assess relevant medications/ vaccinations	Sections5.1.2 and 6.5	X	**X**		**X**	**X**	X	X	X

Visit Type	ClinicVisit	Clinic Visit	**Phone Call**	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Phone Call
Study period	Screening	**Treatment**	**Tre.itment**	**Treatment**	**Treatment**	**Treatment**	Follow- up	Follow- up
Stud y Da y		1	3, 5	4/6	15	29	91	**181**
Visit Window (Days)	-5 to 1	0	2 da ys (-1/+1), 4 days (0/+2) after vacc	3/5 da)'S (-1/+1) after vacc	14 days (-2/+2) after vacc	28days (-7/+14) after Yacc	90 days (-14/+14) **aftel' vacc**	180 days (-14/+14) after vacc
Visit Number	Pre- **vacc.ination**	1	NIA	2	3	**4**	5	***6***
Study Event | References								
Imm unogenicity								
Serology blooddraw | Section 3.5		X"		X		X		
S tu dy C-0mp le rio n **Pt·ocedure**								
StudyTennination' | Section *5.5*								X

Notes :

- Subject will berandomized into a blooddraw schedule in a I: I ratio. Toe second clinic visit will occur at Day 4 OR Day *6*.

b Confirm consent fonn(s) signed prior to any procedures.

' Procedure to be performed prior to vaccination

d If the clinicvisit at Day 4 is overlapping with the specified window of theDay 3 reminder c.ill, the Day 3 reminder call may be omitted. If the clinic visit at Day *6* is overlapping with the specified window of the Day *5* reminder call, the Day *5* reminder call may beomitted.

- Subjects who tenninate the study early are recommended to complete certainstudy-related procedures. See section *5.5* for further details.

LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Tmm1mization Practices
AE	Adverse Event
CI	Confidence Inteival
CBER	Center for Biologics Evaluation and Research
CRM	Cross Reactive material
CRO	Contract Research Organization
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
GSK	GlaxoSmithKline Vaccines
hSBA	Human Serum Bactericidal Assay
1B	Investigator' s Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IM	Intramuscular
IRB	Institutional Review Board
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
pp	Per Protocol
Ref.	Reference
SAE	Serious Adverse Event
SOC	System Organ Class
SOP	Standard Operating Procedure

1. BACKGROUND AND RATIONALE

1.1 Background

Neisseria meningitidis is a leading cause of bacterial meningitis and sepsis worldwide, capable of causing outbreaks and epidemics of invasive disease. Meningococcal disease is associated with high morbidity and mortality even among patients who receive early antibiotic treatment. Most cases of invasive disease worldwide are caused by serogroups A, B, C, W and Y.

The quadrivalent meningococcal oligosaccharide diphtheria CRM-197 conjugate vaccine (MenACWY-CRM; Menveo, GSK Vaccines) is approved for active immunization of individuals from 2 months through 55 years of age in the United States. As of February 2015, more than 30,000 of subjects have been exposed to MenACWY-CRM vaccine in completed clinical studies and more than 24 million doses of the vaccine have been distributed globally.

The US Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination with a quadrivalent conjugated meningococcal vaccine for adolescents at **11-**12 years of age with a booster dose administered 5 years later. While a substantial body of data exists showing a robust immune response and good antibody persistence after a single dose of MenACWY-CRM in adolescents, the response to a booster dose of MenACWY-CRM in this age group has only been evaluated in 2 clinical studies with limited number of subjects.

A robust anamnestic immune response to a booster dose of Menveo vaccine administered at approximately 5 years after previous vaccination with the same vaccine or a licensed meningococcal polysaccharide vaccine (Menomune®) was demonstrated in the phase 2 clinical study V59P6E1 . High titers of bactericidal antibodies against the vaccine serogroups were achieved at 7 and 30 days after booster dose in MenACWY-CRM-primed subjects. However, the number of subjects included in this study was relatively small (N=101, including 50 subjects who received a booster dose after the primary MenACWY-CRM vaccination).

In the phase 3b clinical study V59P13E1, a booster dose of MenACWY-CRM was given 3 years after primary vaccination with either MenACWY-CRM or Menactra® (a meningococcal diphtheria toxoid-conjugated MenACWY vaccine, MenACWY-D) in adolescents. A booster dose was able to substantially increase antibody titers against all 4 serogroups irrespective of the priming vaccine. Again, only small number of subjects (N=160) received the MenACWY-CRM booster, (83 who received primary MenACWY-CRM and 77 who received MenACWY-D).

In the light of the current ACIP recommendation for a booster dose of MenACWY-CRM, there exists a need to evaluate the response to a MenACWY-CRM booster given at - 5 years after primary vaccination in meningococcal-vaccine primed adolescents. Generation of this data would also be of relevance in outbreak management and vaccination of travelers to endemic areas.

1.2 Rationale

The pwpose/aim of this study is to assess the safety and antibody response to vaccination with a booster dose of Menveo given 4-6 years after primary vaccination and the response to a single dose given to vaccine-naive subjects, and to describe the immune response over time after a single dose of Menveo, dminist>red to subjects previously vaccinated with Menveo or Menactra or to vaccine-naive subjects. The inclusion of vaccine-naive subjects in a separate study arm is to enable comparison of the rapidity and magnitude of an anamnestic response to a booster dose (in primed individuals) or the primary response to a first dose (in naive individuals) of MenACWY-CRM.

2. OBJECTIVES

2.1 Plimary Objective(s)

Plimary Immunogeoicity Objective(s)

1. To demonstrate a sufficient immune response following a single dose of MenACWY-CRM (Menveo) vaccine, given to subjects who previously received Menveo or Menactra, as measured by the percentage of subjects with hSBA seroresponse against *N. m.eningitidis* serogroups A, C, W and Y at Day 29 after vaccination

   Criteria to demonstrate immune response sufficiency: The immune response will be considered as sufficient if the lower limit of the one-sided 97.5% CI for percentage of subjects with hSBA seroresponse against serogroups A, C, W and Y is greater than 80% (in pooled group of subjects who received primary vaccination with Menveo or Menactra).

2.2 Second ar y O bjecti ve(s)

Second ar y I mm un og eni city O b je cti ve(s)

1. To compare the immunogenicity of a single dose of MenACWY-CRM vaccine, between subjects who previously received Menveo, subjects who previously received Menactra and vaccine-naive individuals, as measured by the percentage of subjects with hSBA titer ;,:8, with hSBA seroresponse, and hSBA GMTs against *N. meningitidis* serogroups A, C, W and Y at Day 29 after vaccination
2. To compare the immune responses following a single dose of MenACWY-CRM vaccine, between subjects who previously received Menveo, subjects who previously received Menactra and vaccine-naive individuals, as measured by the percentage of subjects with hSBA titer 8 and hSBA GMTs against *N. m.eningitidis* serogroups A, C, W and Y at Day 1, Day 4, Day 6, and Day 29 after vaccination
3. To assess persistence of bactericidal antibodies against serogroups A, C, W and Y at approximately 4-6 years after the primary vaccination with Menveo and after the primary vaccination with Menactra in comparison with naturally-acquired level in vaccine-naive individuals, as measured by the percentage of subjects with hSBA titer 8 and hSBA GMTs at Day 1.
4. To compare the immune response to a single dose of MenACWY-CRM vaccine, between subjects who previously received Menveo, subjects who previously received Menactra and vaccine-naive individuals, by age group (15-25 and ;,:26 years of age), as measured by percentages of subjects with hSBA titer 8, hSBA seroresponse and hSBA GMTs at Day 29.

Secondary Safety Objective(s)

1. To assess reactogenicity and safety of MenACWY-CRM vaccine when administered to subjects who previously received Menveo or Menactra and vaccine-naive individuals.

2.3 Exploratory Objective(s)

There are no exploratory objectives.

3. STUDY DESIGN

3.1 Overview of Study Design

This is a phase 3b, controlled, open-labe multi-center studyto evaluate safety and immunogenicityof MenACWY-CRM after a single vaccination in healthy individuals who were vaccinated with Menveo or Menactra 4 to 6 years ago and in vaccine-naive individuals

Study population: Approximately 700 healthy subjects 15 through 55 years of age willbe enrolled in the study.

Duration of the study: The duration of this studyis approximately 6 months per subject.

Written informed consent and, as applicable according to local guidelines, written assent willbe obtained before conducting anystudy-specificprocedures.

Vaccination schedule: All subjects will receive a single dose of MenACWY-CRM at Day 1.

Study groups:

Group Menveo-Menveo: approximately 300 subjects, who were vaccinated with a single dose ofMenveo 4 to 6 years ago, will receive one dose of MenACWY-CRM.

Group Menactra-Menveo approximately 300 subjects, who were vaccinated with a single dose of Menactra 4 to 6 years ago, will receive one doseof MenACWY-CRM.

Group Naive: approximately 100 subjects equally enrolled across all clinical sites, who have not received any meningococcal vaccination, will receive one dose of MenACWY-CRM.

Randomization / Stratification:

Within each study group, subjects will be enrolled across age range of 15 to 55 years of age as follows:

- Menveo-Menveo and Menactra-Menveo groups: approximately 80% of subjects will be enrolled in age groupof 15 to 25 years and 20% of subjects will be enrolled in 26-55 years age group.
- Naive group: approximately 50% of subjects willbe enrolled in age groupof 15 to 25 years and 50% of subjects will be enrolled in age group of26-55 years.

Within each age category in each study group, subjects will be randomized into one of two different blood draw schedules according to a 1:1 ratio, described as follows:

- Subjects getting blood draws at Day 1, Day 4 and Day 29.
- Subjects getting blood draws at Day 1, Day 6 and Day 29.

For a schematic overview, see Table 1

Table 3.1-1: Schematic diagram of the V59_77 study groups

Vaccine History	Vaccination in current study	Age Category	Blood draw schedule
Menveo N=300	Menveo	15-25 years (N=240)	Blood draw Day 1, 4, 29 (N=120)
			Blood draw Day 1, 6, 29 (N=120)
		26-55 years (N=60)	Blood draw Day 1, 4, 29 (N=30)
			Blood draw Day 1, 6, 29 (N=30)
Menactra N=300	Menveo	15-25 years (N=240)	Blood draw Day 1, 4, 29 (N=120)
			Blood draw Day 1, 6, 29 (N=120)
		26-55 years (N=60)	Blood draw Day 1, 4, 29 (N=30)
			Blood draw Day 1, 6, 29 (N=30)
Vaccine-Naive N=100	Menveo	15-25 years (N=50)	Blood draw Day 1, 4, 29 (N=25)
			Blood draw Day 1, 6, 29 (N=25)
		26-55 years (N=50)	Blood draw Day 1, 4, 29 (N=25)
			Blood draw Day 1, 6, 29 (N=25)

Blinding- open-label study.

Blood samples: Three (3) blood samples of approximately 10 mL each will be collected according to the blood draw schedule in Table 3.1.1.

Data collection: Electronic Case Reporting Form (eCRF).

Study clinic visits: Three (3) clinic visits at Day 1, Day 4 or Day 6 and Day 29 are planned for each subject.

Reminder Phone calls: Two (2) reminder phone calls will be conducted at Day 3 and Day 5 after the study vaccination to remind the subject/ legal guardian to complete the diary card.

Safety phone calls: Three (3) safety phone calls (at Day 15, Day 91 and Day 181) will be conducted to collect any medically-attended AEs, AEs leading to withdrawal, SAEs,

related medications and any vaccinations. In addition, all unsolicited AEs and related medications occurring after the vaccination will be collected during the safety call at Day 15. The Day 181 Safety Phone call will also serve as the termination visit

Solicited Adverse Events (injection site pain, erythema, induration, fatigue, headache, myalgia, arthralgia, loss of appetite, nausea, chills and fever) occurring on the day of vaccination and the following six days (Day 1 through Day 7) will be recorded daily using a Diary Card for all subjects.

Unsolicited AEs occurring within 28 days after study vaccination will be collected. Qualified site staff will interview the subject by phone approximately 14 days after vaccination and in person at the study site approximately 28 days after study vaccination to assess the occurrence of any unsolicited AEs.

Medically-attended AEs AEs leading to study withdrawal and SAEs will be collected during the entire study period. These data will be captured by interviewing the subject and/or subjects' parents / guardian (as applicable) during the site visits and phone calls and by review of available medical records. Subjects and/or parents / guardian will be encouraged to call the site in the event of any medically-attended AEs or any AEs which they perceive as being of concern during the entire study period.

Table 3.1-2: Schematic diagram of the V59_77 study design

Day 1	Day 4	Day 6	Day 15	Day 29	Day 91	Day 181
Blood draw (all subjects) Menveo	Blood draw (50%)	Blood draw (50°/c,)	Safety Phone call	Blood draw (all subjects)	Safety Phone call	Safety Phone call Study termination

3.2 Study Period

Each subject should expect to participate in the study for 6 months, from the time of enrolment through the last study visit.

3.3 Blinding Procedures

The trial is designed as an open-label study.

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/Vaccinations
- Information on the blood samples.

All data collected must only be identified using the Subject ID, as described in section S.1.4, Randomization.

3.4.2 Tools Used for Data Collection

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

Subject Diary

Paper Diaries (pDiaries), hereafter referred to as Subject Diaries will be the only source document allowed for solicited local and systemic adverse events (including body temperature measurements), starting after the initial, 30 minute post-vaccination period at the clinic. The following additional rules apply to documentation of safety information collected in the Subject Diary.

The Investigator or delegated staff should monitor the Subject's Diary status throughout the study for compliance and any solicited local and systemic adverse events that were of concern to the subject

- No corrections or additions to the information recorded by the subject or parent(s)/legal guardian(s) within the Subject Diary will be allowed after it is delivered to the site.
- Any blank or illegible fields on the Subject Diary must be described as missing in the eCRF.

Case Rep01t Forms

This study utilizes electronic Case Report Forms (eCRFs) to collect study-related data from each subject. A qualified site staffmember(s) is required to enter subject data in the eCRFs in English based on the medical information available in each subject' s source record.

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

The following additional rules apply to documentation of Subject Diary information collected in the eCRFs:

- The site must enter all readable entries in the Subject Diary into the eCRF, including those values that may be biologically implausible (e.g. bodytemperature: 400°C).
- Any illegible or implausible data should be reviewed with thesubject and/or parent(s)/legal guardian(s). 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 eCRF (e.g., if the subject above confinns 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 eCRF).
- Any newly described safety information (including a solicited adverse event) nrust not be written into the Subject Diary andnrust 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 EventeCRF.

3.5 Collection of Clinical Specimens

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

- Blood.
- Urine for pregnancy testing (As per routine practice, specimens will betested at each site).

Processing of a specimen should be completed bya qualified site member and in accordance with the study-specificClinical Specimen Laboratory Manual. Testing of serum specimens will be performed by a GSK or a designated laboratory. Refer to the study-specific Clinical Specimen Laboratory Manual for additional details.

Blood Specimens

Approximately 10 mL sample of blood will be drawn from all subjects at visit Day 1 before vaccination, and at visit Day 4 or Day 6 and Day 29. The blood volume will not exceed 10mL at each time point in order to provide the necessary serum volume (approximately half of the blood draw volume) for the serology assays.

The blood will be used for inummologial assays See section 7, Assessments for additional details.

The total ammmt of blood collected over the study period per subject will be approximately 30mL.

U1in e S p eci m e ns

Urine will be collected for pregnancy testing in females of child bearing potential. Urine will be collected at visit Day 1 before vaccination and the results recorded in the source document and eCRF.

3.6 Stopping/Pausing Guidelines

There are no predetermined stopping rules in this study. Subjects may be withdrawn from the study according to investigator discretion as described in section 3.8, Premature Withdrawal from Study.

3.7 Data Monitming Committee

No DMC will be utilized for the study.

3.8 Premature \Vithdrawal 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 nrust 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 before or 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 S.5.1, Early Termination Visit 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 nrust be identified on the AE eCRF page by indicating "Withdrawn from study due to AE". Any ongoing AEs at the time of studywithdrawal must be followed until resolution or stabilization

Death

For anysubject withdrawn from study participation due to death, this should be noted on the StudyTermination eCRF page and the associated SAE that led to the death must be reported.

, v ithdrawal ofconsent

The subject and/or parent(s)/legal guardian(s) 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 and/or parent(s)/legal guardian(s) intends to withdraw consent from the study, the investigator should clarify if the subject will withdraw completely from the study or if the subject willcontinue 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.

If a subject and/or parent(s)/legalguardian(s) withdraws consent but does not revoke the HIPAA authorization, the Sponsor will have fullaccess to the subject's medical records, including termination visit information. If a subject and/or parent(s)/legal guardian(s) revokes only the **HIPAA** authorization, the Sponsor will have fullaccess to all of the subject's medical records prior to the date and time of written revocation.

Lost to Follow-Up

For subjects who fail to show up for finalvisits (clinic or telephone contacts), or for three consecutive visits, study staff are 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 and/or parent(s)/legal guardian(s) to encourage the completion of study termination procedures. These efforts to contact the subject should be recorded in the source document. The termination date for the subject to be captured on the Study Termination eCRF page is the date of the last successful contact (clinic visit or telephone) withthe subject.

Administrative Reason

Examples for subjects withdrawn from the study due to administrative reason can include: Sponsor decision to terminate the study, subject discontinuation for insurance issues, moving, no time, etc. This reason should be noted in the StudyTermination eCRF page and any ongoing AEs at the time of studywithdrawal should be followed until resolution/stabilization, if possible.

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 StudyTermination eCRF 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 studythis 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, despite the protocol requirement for adequate contraception should be encouraged to continue participating in the study for

safety follow-up only. The site nrust complete a Pregnancy Report CRF (initial report) as soon as possible after learning of pregnancy occurrence (see section 7.1.6, Pregnancies for further details). If the subject withdraws fromthe study for any of the above categories except death, the sitewill 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 follow-up period.

3.9 End of Study

Most clinical trials intended to support the efficacy/immunogenicityand safety of an Investigational Product proceed to fullcompletion of planned sample size accrual.

Evaluation of the primary and/or secondary immunogenicity/efficacyobjectives requires the testing of biological samples from the 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 the last clinic visit, Day 29. 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 Day 29 visit

If the completion of testing occurs prior the completion of the Last Subject Last Visit (LSLV) the latter date defines the end of study visit

4. SELECTION OF STUDY POPULATION

4.1 Inclusion C1iteria

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

1. Individuals of IS through SS years of age on the day of informed consent or assent.
2. Individuals who received Menveo 4 to 6 years prior to enrollment at an age of 11 years or older (Menveo-Menveo group)

   OR

   Individuals who received Menactra 4 to 6 years prior to enrollment at an age of 11 years or older (Menactra-Menveo group)

   OR

   Individuals who have not received any previous meningococcal vaccine (Naive group).
3. Individuals who have voluntarily given written informed consent *or* assent after the nature of the study has been explained according to local regulatory requirements, prior to study entry. If the subject is under age 18 at the tinie of enrollment, the parent(s)l1egal *guardian(s)* of the subject should have voluntarily given written informed consent.
4. Individuals who can comply with study procedures including follow-up.[2]

S. Males

Or

Females of non-childbearingpotential[3]

Or

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[2] A subject and/or parent(s)/Jegal guardian(s) is/are considered to be compliant if the Investigator judges that the subject will complete the Subject Diary and return for all the follow-up visits scheduled in the study.

[3] A female is considered to be of non-childbearingpotential prior to menarche and after natural or induced menopause. Natural menopause is recognized to have occuned after 12 consecutive months of amenorrhea for which thereis nootherobvious pathological or physiologicalcause. Induced menopause is recognized to have occurred after hysterectomy, after bilateral oophorectomy, or iatrogenic ablation of ovarian ftmction.

Females of childbearing potential who are using aneffective birth control method[4] which they intend to use for at least 30 days after the last study vaccination.

4.2 Exclusion Crite1i a

Each subject must not have:

1. History of any meningococcal vaccine administrationother than the single vaccination given at4 to6 years ago (Menveo-Menveo and Menactra-Menveo groups)

   OR

   History of any meningococcal vaccine administration (Naive group)

2. Current or previous, confirmed or suspected disease caused by *N. meningitidis*.
3. Household contact with and/or intimate exposure to an individual with any laboratory confirmed *N. meningitidis* infection within 60 days prior to study vaccination.
4. Progressive, unstable or uncontrolled clinical conditions.

S. Hypersensitivity, including allergy, to any component of vaccines, medicinal products or medical equipment whose use is foreseen in this study.

6. Clinical conditions representing a contraindication to intramiscular vaccination (IM) andblood draws.
7. Abnormal function of the iimnune 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 study vaccination.
   c. Administration of antineoplastic and iimnunomodulating agents or radiotherapy within 90 days prior to study vaccination.

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[4] The following birth control methods areconsidered effective:
Abstinence
Hormonal contraceptive (such asoral, injection, transdennal patch, implant) if used for at least 30 days prior to informed consent
Diaphragm preferably with spermicide, tubal occlusiondevice
Intrauterine device (IUD)
Tubal ligation
Male par1ner using condom preferably with spermicide
Male par1ner having been vasectomized at least six months prior toinformed consent

8. Received immunoglobulins or any blood products within 180 days prior to informed consent.
9. Received systemic antibiotic treatment within 3 days prior to study vaccination or blood draw.
10. Received an investigational or non-registered medicinal product within 30 days prior to study vaccination .
11. Study personnel as an immediate family or household member.
12. Individuals who have received any other vaccines within 7 days (for inactivated vaccines) or 14 days (for live vaccines) prior to vaccination in this study or who are planning to receive any vaccine within 28 days from the study vaccination.
13. Individuals who have experienced a moderate or severe acute infection and/or fever defined as a temperature 38°C (100.4°F) within 3 days prior to study vaccination.
14. Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the subject due to participation in the study.

4.3 Clitelia for Delay of Vaccination and/or BloodSampling

There may be instances when individuals meet all eligibility criteria for vaccination yet have a transient clinical circumstance which may warrant delay of vaccination: body temperature elevation [38.0° C 100 .4° F) within 3 days prior to intended study vaccination], systemic antibiotic treatment within 3 days prior to study 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.

There is a clinical circumstance that warrants delay of blood collection for immunogenicityassessments in this study. This situation is listed below. In the event that a subject meets this criterion for delay of blood collection, blood collection may proceed once the window for delay has passed.

Subject has received a dose of systemic antibiotics lessthan 3 days before the intended blood collection.

5. 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 Table4.

Table 5-1 Study Procedures

Visit Category	Procedures
Pre-vaccinationClinic Visit(s)	Section 5.1 describes procedures to befollowed prior to study vaccination: informed coosent/assent, screening, enrolment, andrandomization
VaccinatiooClinic Visit(s)	Section 5.2 describes procedures to befollowed during each clinicvisit involving vaccination: vaccination, post-vaccination procedure,sand post-vaccination reminders
Post-vaccination Visit(s)	Section 5.3 describes follow-upclinic visits and safety follow-up calls
Unscheduled Visit(s)	Section 5.4 describes possible procedures to be followed at unscheduled clinic visit
Study Termination Visit	Section 5.5 describes procedures to befollowed at the last study visit for a subject (mayinclude early termination visit)

5.1 Pre-vaccination Clinic Visit(s)

This section describes the procedures that must be performed for each potential subject prior to vaccination, including obtaining informed consent/assent, screening, enrolment and randomization.

5.1.1 Informed Consent/Assent

"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 willof 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.

"Assent" is a term used to express willingness to participate in research by persons who are by definition too young to give informed consent but who are old enough to understand the proposed research in general, its expected risks and possible benefits, and

the activities expected of them as subjects. Assent by itself is not sufficient, however. If assent is given, informed consent must still be obtained from the subject's parent(s) or legal guardian(s). Local laws define who constitutes a "child," and such definitions dictate whether or not a person can legally consent to participate in a protocol (Levine 1988).

Infonned consent of the parent(s)/legal guardian(s) and assent of subject following local !RB/EC guidance **must** be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent and assent should be documented in the subject source document in addition to maintaining a copy of the signed and dated informed consent. Additional specifics regarding the informed consent and assent processes are located in section 13.2, Infonned Consent Procedures.

If a subject and/or parent(s)/legalguardian(s) is unable to read, an impartial witness should be present during the entire informed consent and assent discussion. An impartial witness is defined as a person who is independent from study conduct, who cannot be unfairly influenced by those involved with the study, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject and/or parent(s)/legal guardian(s) and after the subject and/or parent(s)/legal guardian(s) has verbally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the infonned consent fonn, the witness should sign and personally date the consent form. By signing the consent fonn, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject and/or parent(s)/legal guardian(s) and that informed consent was freely given by the subject and/or parent(s)/legal guardian(s).

5.1.2 Screening

After an individual has consented to participate in the study and infonned consent/assent is signed, that individual will begiven a unique Screening Number manually created by the investigator. The subject' s unique Screening Number will bedocumented in the Screening and Enrolment log. The eligibility of the subject will bedetermined based on the inclusion and exclusion criteria listed in section 4, Selection of Study Population and evaluated during this screening procedure.

Prior to study enrolment, demographic data willbecollected from the subject, including: date of birth, gender, race, ethnicity, prior vaccination against meningitis.

Medical history will also be collected, including but not limited to any medical history that may be relevant to subject eligibility for study participation such as prior vaccinations, concomitant medications, and previous and ongoing illnesses or injuries. 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.

Review of systems is a structured interview that queries the subject and/or parent(s)/legal guardian(s) as to any complaints the subject has experienced across each organ system This will be performed before enrolment and used to guide physical examination.

If applicable, prior and concomitant medications or vaccinations taken prior to start of study should be collected (refer to section 6.5, Prior and Concomitant Medications and Vaccines for further details).

Collect vital signs (heart rate, blood pressure, and temperature (preferably taken orally). Measure height and weight.

Perform pregnancy testing in women of childbearing potential (refer to section 3.5, Collection of Clinical Specimens for additional information)

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.

The data collected through study assessments listed above will be written in the source document (see section 9.1, Source Documentation). Should the physical assessment reveal any abnormal values or events, these must be documented in the CRF Adverse Events Form

Prior to vaccination, approximately 10 mL of blood will be drawn from all subjects for the immunological testing see section 3.5, Collection of Clinical Specimens.

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 will be enrolled into the study.

5.1.3 Em·olment

After signing the informed consent/assent fonn, if an individual is determined to be eligible for study participation, the investigator will emoll the subject.

5.1.4 Randomization

Upon entering subject demographic data in IRT, the system will assign a 7 digit subject ID number consisting of the 3 digit site number and 4 digit order of randomization at the site. Access to IRT can be obtained by the site staff either via web or telephone (as back up). The Subject ID will be the subjec'ts unique identification number for all CRFs and associated study documentation that will be used for duration of the study. After randomization, the Screening Number ceases to be used and remains in the Screening and Enrolment Log only.: During the randomization transaction in IRT Subjects will be assigned a kit number for Menveo vaccination and will be randomized to a blood draw schedule (1:1 according to age group and previous vaccination status). The list of randomization assignments is produced by the IRT service provider and approved by GSK Randomization Office according to applicable GSK Standard Operating Procedure (SOP).

IRT will also be used to ensure adequate and appropriate distribution of enrolment of naive subjects across all sites. Further details may be found in study-specific plans, for eg, the IRT User Manual and the Randomization Configuration Document.

If for any reason, after signing the info11lled consent form (ICF), the subject who is eligible and enrolled fails to be randomized, this is called a randomization failure and 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 (SDA). 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, Screening.

If for any reason, after randomization the subject fails to undergo treatment, this is an Early Termination and the reason should be recorded in source document as specified in the SDA. The information on these Early Termination subjects should be kept distinct in the source documentation from randomization failures.

Within each study group, subjects will be enrolled across age range of 15 to 55 years of age as follows:

- Menveo-Menveo and Menactra-Menveo groups: approximately 80% of subjects will be enrolled in age group of 15 to 25 years and 20% of subjects will be enrolled in 26-55 years age group;
- Naive group: approximately 50% of subjects will be enrolled in age group of 15 to 25 years and 50% of subjects will be enrolled in age group of 26-55 years.

Within each age category in each study group, subjects will be randomized into one of two different blood draw schedules according to a 1:1 ratio, described as follows:

- Subjects getting blood draws at Day 1, Day 4 and Day 29.
- Subjects getting blood draws at Day 1, Day 6 and Day 29.

If for any reason, after enrolment the subject fails to undergo treatment/study procedures this is an Early Tennination and the reason should be recorded in source document as specified in the Source Data Agreement (SDA). The information on these Early Termination subjects should be kept distinct in the source documentation from subjects who are screen failures, as described in section S.1.2, Screening.

5.2 Vaccination Clinic Visit

The first vaccination will be performed on Day 1.

For studies which have visits for concomitant vaccinations or treatments, see section 6.5, Prior and Concomitant Medications and Vaccines for those visit procedures.

Ensure all blood samples are taken **p1i or** to the vaccination.

After completing the pre-vaccination procedures on day 1, administer the vaccine to the subject according to the procedures described in section 6.3, Vaccine Preparation and Administration. Observe the blinding procedures described in section 3.3, Blinding Procedures.

Prior to administrationof study vaccination, confirm that the subject does not meet any criteria for delaying additional study vaccinations as described in section 4, Selection of Study Population.

5.2.1 Post-vaccination Procedures

The following post-vaccination procedures will be performed on day 1.

- After vaccination, the subject will be observed for at least 30 minutes including observation for unsolicited adverse events, solicited adverse events, and body temperature measurement. Record all safetydata collected during this time in the subject's source document.
- A Subject Diary will be used in this studyto document solicited adverse events. The Subject Diary is the only source for collection of these data; therefore, it is critical that the subject completes the Subject Diary correctly. The subject should be trained on how and when to complete each field of the Subject Diary.

- The subject and/or parent(s)/legal guardian(s) should be trained on how to self-measure local solicited adverse events. The measurement of solicited local adverse events is to be performed using the ruler provided by the site.
- The subject and/or parent(s)/legal guardian(s) 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 and/or parent(s)/legal guardian(s) 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 and/or parent(s)/legal guardian(s), but if a person other than the subject and/or parent(s)/legal guardian(s) enters information into the Subject Diary, this person's identity must be documented in the Subject Diary or subject's source record. Any individual that makes entries into the Subject Diary must receive training on completion of the Subject Diary at the time of the visit. This training must be documented in the subject's source record.

The same individual should complete the Subject Diary throughout the course of the study.

- The site should schedule the next study activity clinic visit on Day 4 or Day 6 depending to which blood draw schedule subject was randomized to with the subject and/or parent(s)/legal guardian(s).

The subject and/or parent(s)/legal guardian(s) will be reminded to complete the Subject Diary and to contact the site if there are any questions, and to contact the site inunediately (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 or to a visit to/by a doctor or is of concern.

5.2.2 Post-vaccination Reminders

Reminder calls or alerts are not intended to be an interview for collection of safety data. If the subject and/or parent(s)/legal guardian(s) wishes to describe safety information, this information should only be collected by a healthcare professional at the site, and the safety data described must be written down in the subject's medical chart.

Subject Diary Reminder Calls

Subject Diary reminder calls will be performed on day 3 and day S. The purpose of this call is to remind the subject and/or parent(s)/legal guardian(s) about completion of the

Subject Diary. The call follows the Subject Diary Reminder Telephone Call Script provided to the site. The subject and/or parent(s)/legalguardian(s) should be reminded to contact the site via the telephone number provided in the informed consent to discuss medical questions. If the clinic visit at Day 4 or Day 6 overlaps with the specified window of the Day 3 or Day 5 reminder call, the Day 3/Day 5 reminder call maybe omitted.

5.3 Post-vaccination Visit(s)

Post-vaccinationvisits will be performed on Day 4 or Day 6according to the blood draw schedule to which subject was randomized and Day *29*.

5.3.1 Follow-up Clinic Visit(s)

Follow-upclinic visits will be performed on Day 4 or Day 6 according to the blood draw schedule to which subject was randomized and on Day 29.During the follow-up clinic visit:

- Subject Diary will be reviewed at Day 29. No changes to the information recorded within the Subject Diary are permissible. For details on the Subject Diary see sections 3.4.2, Tools Used for Data Collection and 5.2.1, Post-vaccinationProcedures. The subject and/or parent(s)/legal guardian(s) 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. This interview will follow a script which will facilitate the collection of relevant safety information. 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. Adverse events reported by the subject and/or parent(s)/legal guardian(s) at this follow-up clinic visit must be recorded in the subject's source document and on an Adverse Events CRF, as specified in section 7.1, Safety Assessment, and not written on the script used for the interview.
- Performa brief symptom-directed physical examination if necessary according to symptoms the subject has reported. This is a physical examination that will include an examination of organ systems that are relevantto the investigator based on review of the subject's reported adverse events, concomitant medication use. This assessment may include: measurement of vital signs, body temperature and a check of general appearance. The physical assessment must be performed by the investigator or designee of the investigator, who is qualified to perform a physical assessment in accordance with their institutional policy. Corresponding information is documented in the subject' s source document and CRF(s).
- Collect a blood sample (see section 3.5, Collection of Clinical Specimens for additional information).

The site should schedule the next study activity safety call with the subject and/or parent(s)/legal guardian(s).

The subject and/or parent(s)/legal guardian(s)] will receive a written reminder of the next planned study activity. The subject and/or parent(s)/legal guardian(s) 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 call will be performed on Day 1S, Day 91 and Day 181.

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 and/or parent(s)/legal guardian(s) will be interviewed according to the script, and information related to unsolicited adverse events (only at Day 1S), serious adverse events (SAEs), medically attended adverse events, AEs leading to withdrawal and concomitant medications or vaccinations associated with those events will be reviewed. 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 with the subject and/or parent(s)/legal guardian(s).

The subject and/or parent(s)/legal guardian(s) 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

Unscheduled visits are not expected within this protocol.

5.5 Study Termination Visit

The study termination visit will occur on Day 181. The termination visit will be a telephone call. The date of termination is the date of the last contact (clinic visit or telephone call) 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, Early Termination Visit.

During the telephone call, the following procedures will be performed: interview of subject and/or parent(s)/legal guardian(s) to collect medically attended adverse events, AEs leading to withdrawal, SAEs, as well as interview of subject and/or parent(s)/legal guardian(s) to collect concomitant medications/ vaccinations associated with those events. All safety information described by the subject nrust be written down in a designated location within the source document and not written on the script used for the telephone call.

The site will review with the subject and/or parent(s)/legal guardian(s) the plan of when infonnation 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 and/or parent(s)/legalguardian(s) chooses to share this infonnation.

The sitewillcomplete 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 notifythe Sponsor and, when possible, will perform the procedures listed below. The reason(s) for the early termination will be included in the subject' s source documentation. If the EarlyTermination Visit is a telephone call, collect as much infonnation 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 will be performed: interview of subject and/or parent(s)/legal guardian(s) to collect adverse events, medically attended adverse events, AEs leading to withdrawal, SAEs, interview of subject and/or parent(s)/legalguardian(s) to collect concomitant medications/ vaccinations.

The site will review with the subject and/or parent(s)/legal guardian(s) the plan of when infonnation 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 and/or parent(s)/legalguardian(s) chooses to share this infonnation.

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

6. 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 p1ior 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 below. The study vaccines specific to this study is the **MenACWY-CRM** vaccine (Menveo® , GSK) .

The Meningococcal ACWY conjugate vaccine is obtained by extemporaneous mixing just before injection of the lyophilized MenA-CRM component with the MenCWY-CRM fullliquid vaccine. The pharmaceutical form is Powder and solution for solution for injection. Menveo® is provided as vial/vial presentation. MenA lyophilised conjugate component (glass vial) and MenCWY liquid conjugate component (glass vial). After reconstitution, MenACWY-CRM will have the following composition per O.S mL of injectable solution (SeeTable 6.1-1):

Table 6.1-1: MenACWY-CRM Composition

Name of Ingredient	Unit and/or Percentage Formula (Dose 0.5 mL)
Drug Substances	
CRM197-MenA conjugate	10 µg MenA, 16.7-33.3 µg CRM197
CRM197-MenC conjugate	5 µg MenC, 7.1-12.5 µg CRM197
CRM197-MenW conjugate	5 µg MenW, 3.3- 8.3 µg CRM197
CRM197-MenY conjugate	5 µg MenY, 5.6- 10 µg CRM197
Sodium chloride	4.5mg
Excipients	
Sucrose	12.5 mg
Sodium phosphate buffer Sodium dihydrogen phosphate Disodium hydrogen phosphate dehydrate	10mM 2.5mM 7.5mM
Potassium dihydrogen phosphate	5mM
Water for Injection	q.s 0.5 mL
Volume of Formulation	0.6mL
Appearance	Colorless to light yellow
Vaccine Presentation	A single dose of two vials

One 0.5 mL dose of MenACWY will be administered by intramuscular (IM) injection in the deltoid area of non-dominant arm (preferably).

For more detailed information, refer to the latest version of Investigator Brochure and SPC for Menveo®, which are included in the investigator site file.

6.2 Non-Study Vaccines

Not applicable.

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 personnel who are qualified to perform that function under applicable local laws and regulations for the specific study site.

All study vaccines to be administered to the subjects must be stored in a safe and locked place with no access by unauthorized personnel.

The study vaccines will be stored at the defined temperature range (i.e. +2 to +8C). The storage temperature of the vaccines will be monitored daily with temperature monitoring devices and will be recorded.

Any temperature deviation, i.e. temperature outside the range (+2 to +8°C), must be reported to the sponsor as soon as detected. Following the exposure to such a temperature deviation, vaccines will not be used until written approval has been given by the sponsor.

The study vaccine should be allowed to reach room temperature before administration, according to local vaccination practice.

MenACWY-CRM (Menveo) vaccine is prepared by aseptically withdrawing all fluid from the vial containing the MenCWY-CRM liquid conjugate component and injecting the liquid into the vial containing the MenA-CRM lyophilized portion. Invert and shake the vial well until the vaccine is dissolved. The final mixed vaccine is then ready for administration of the MenACWY fornrulation (0.5 mLJ dose of injectable solution).

Detailed vaccine preparation and administration instructions will be provided to investigators in the Protocol Ancillary Document prior to study start.

PRECAUTIONS TO BE OB SERVE D 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 arlroinislTation is determined by evaluating the entry criteria outlined in protocol sections 4.1, Inclusion Criteria and 4.2, Exclusion Criteria.

Eligibility for non-study vaccines should be determined by the investigator, pending the review of the package insert of the relevant vaccine.

Study vaccines should 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 should 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 Adminish·ation En or 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 Plior and Concomitant Medications and Vaccines

All medications, vaccines and blood products taken or received by the subject within 30 days prior to the start of the study are to be recorded on the Prior and Concomitant Medications CRF.

In addition, the following are considered prior medications for this protocol: all medication/vaccines described in the inclusion and exclusion criteria of this protocol including:

- Systemic administration of corticosteroids (PO/IV/IM) for more than 14 consecutive days within 90 days prior to study vaccination;
- Administration of antineoplastic anrl imm1momodulating agents or radiotherapy within 90 days prior to study vaccination;
- Tmmnonglobulins or any blood products within 180 days prior to informed consent;
- Systemic antibiotic treatment within 3 days prior to study vaccination or blood draw;
- Any investigational or non-registered medicinal product within 30 days prior to study vaccination;
- Administration of vaccines within 7 days (for inactivated vaccines) or 14 days (for live vaccines) prior to vaccination in this study or who are planning to receive any vaccine within 28 days from the study vaccination

Use of analgesics/antipyretics to prevent or treat solicited AEs will be captured in the Subject Diary from day 1-7 following each vaccination. 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.

Concomitant medications include all prescription and non-prescriptionmedications (including vaccines) taken by/administeredto the subject during the 30 days after study vaccination and nrust be documented on the Concomitant Medications CRF. Mineral supplements and vitamins are not considered concomitant medications.

When recording concomitant medications/vaccines, they should be checked against the study entry and continuation criteria in section 4, Selection of Study Population to ensure that the subject should be enrolled/continue in the study.

Concomitant medication dministered for treatment of AEs with medically-attended visits, AEs leading to study withdrawal and SAEs must be documented during the entire study period.

Any vaccine not foreseen in the studyprotocol in the period starting at Day 1 and ending at Day 181 must be recorded in the eCRF.

6.6 Vaccine Supply, Labeling, Storage and Tracking

The Sponsor will ensure the following

- Supply the study vaccine(s).
- Appropriate labeling of all studyvaccines provided that corq>lies 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 studyvaccines, 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:

Not use of vaccines prior to receipt of authorization for use from the Sponsor.

Use only in accordance with the approved protocol

Proper han dling, 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. 1bis 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 or to the Depot for destruction.

7. ASSESSMENTS

7.1 Safety Assessment

The measures of safety used in this study are routine clinical procedures. They include a close vigilance for, and stringent reporting of, selected local and systemic adverse events routinely monitored in vaccine clinical 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 investigaitonal 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 of 180 days 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 source document. 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 and/or parent(s)/legal guardian(s) for 7 consecutive days, using a pre-defmed Subject Diary.

The following solicited adverse events are included in the Subject Diary. Each adverse event is to be assessed using the scoring system reported in parentheses below:

Solicited LocalAdverseEvents

Injectionsite pain, erythema, induration, Solicited Systemic Adverse Events

Fatigue, headache, myalgia, arthralgia, loss of appetite, nausea, chills and fever.

Table 7.1.1-1 Severity grading for solicited local and systemic AEs

	]',fil d	**Moderate**	**Se.vel'e**
Pain	No interference with dailyactivity	Interfereswith daily activity	Prevents daily activity
Erythema	25-50mm	51- IOOmm	> 1 OOmm
lnduration	25-50 mm	51- IOOmm	> 1 OOmm
Fa ti gue	No interference with dailyactivity	Interfereswith daily activity	Prevents daily activity
Headache	No interference with activity	Interfereswith daily activity	Prevents daily activities
Myalgia	No interference with activity	Interfereswith daily activity	Prevents daily activities
Arthralgja	No interference with activity	Interferes with daily activity	Prevents daily activities
Loss ofa ppetite	Eating less than usual with no effect on normal activity	Eating less thanusual / interfered with normal activity	Not eating at all
Nausea	No interference with dailyactivity	Interferes with daily activity	Prevents daily activity
Chills	No interference with activity	Interfereswith daily activity	prevents daily activities

Fever is defined and measured by a body temperature 38.0°C(100.4F). Route of temperature measurement is preferably oral.

Other Indicators of Reactogenicity:

- Use of analgesics / antipyretics for prophylaxis (Days 1-7)
- Use of analgesics / antipyretics for treatment (Days 1-7)
- Body temperature, described in degrees Celsius and summarized by route of measurement and in *05°C* increments from 36.·oc.

The study staff must review the data entered into the Subject Diary as described in section 3.4.2, Tools Used for Data Collection and section S.3.1, Follow-up Clinic Visit(s).

Note: Anysolicited adverse event that meets any of the following criteria must be entered into subjects' source document(see section 9.1, Source Documentation) and also as an adverse event on the Adverse Event CRF:

- Solicited local or systemic adverse event that continues beyond day 7 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, Evaluation of Adverse Events).
- Solicited local or systemic adverse event leading to thesubject withdrawing fromthe study or the subject being withdrawn from the study by the investigator (adverse event leadingto withdrawal, see section 7.1.3, Evaluation of Adverse Events).
- Solicited local or systemic adverse event that otherwise meets the definition of a serious adverse event (see section 7.1.4, Serious Adverse Events).

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 bya subject and/or parent(s)/legal guardian(s) who has signed the informed consent.

Potential unsolicited AEs may be medically attended (defined as symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a health care provider,) or were of concern to the subject and/or parent(s)/legal guardian(s). In case of such events, subjects and/or parent(s)/legal guardian(s) will be instructed to contact the site as soon as possible to report the event(s). The detailed information about the reported unsolicited AEs willbe collected by the qualified site personnel during the interview and will be documented in the subject's records.

Unsolicited AEs that arenot medically attended nor perceived as a concern by subjects and/or parent(s)/legal guardian(s) will be collected during interview with the subject [and/or parent(s)/legalguardian(s) and by review of available medical records at the next visit (see section 5.3, Post-vaccination Visit(s).

7.1.3 Evaluation of Adverse Events

Everyeffort 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 "otitismedia").

Theseverity of events reported on the Adverse Events CRF willbe determined by the investigator as:

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

The relationship of the studytreatment to an AE will be determined by the investigator basedon 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 administrationof 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 studytreatment to an unsolicited AE will be determined by the investigator.

Note: solicited AEs will not be evaluated for relationship to studytreatment. Grading for severity of solicited local and systemic AEs is described in section 7.1.1, Solicited Adverse Events.

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.
- AEs leading to withdrawal: adverse events leading to study or vaccine withdrawal.

If solicited or unsolicited adverse events have been reported and the subject and/or parent(s)/legalguardian(s)] indicated that the symptoms required medical attendance or were of concern, the subject and/or parent(s)/legalguardian(s) must be contacted for further information.

When the subject and/or parent(s)/legal guardian(s) is contacted for any of these reasons, the contact must be documented in thesubject's source documentation.

All AEs, regardless of severity, willbe 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 bemonitored 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 The investigator's assessment of ongoing Adverse Events at the time of each subject's last visit should be documented in the subject's medical chart.

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 theopinion of the investigator, at immediate risk of death from the event as it occUITed); it does not refer to anevent which hypothetically tnight have caused death if it were more severe.
- Required or prolonged hospitalization.
- Persistentor 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, bydefinition, 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 studyvaccine. SAEs that are judgedto be possibly or probably related to the studyvaccine should be reported to the Sponsor as related/suspected events.

The relationship of the studytreatment 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 section7.1.3, Evaluation of Adverse Events).

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 studyvaccine 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 cUITent 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 occUITed 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 hospitalizationwould 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

Adverse Events of Special Interest (AESis) will not be assessed during the study.

7.1.S Methods for Recording Adverse Events and Se1ious Adverse Events

Findings regarding Adverse Events must be reported on an Adverse Events CRF, as specified in section 7.1.1, Solicited Adverse Events, and on the VSAE form, if applicable, which is part of the Investigator Site File. All findings in subjects experiencing AEs nrust be reported also in the subject's source document.

All SAEs which occur during the course of the study, whether considered to be associated withthe study vaccination or not, must be reported within 24 hours of the site becoming awar e of the event to GSK or its designee. Specific instructions and contact details for collecting and reporting SAEs to GSK willbeprovided 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 berecorded 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 willcontact 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/ IRB 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 willcommunicate the information to the investigator and the investigator will be responsible for submitting this infonnation to the EC/IRB and other relevant authorities.

7.1.S.1 Post-Study Events

Any SAE that occurs outside of the protocol-specifiedfollow-up period and considered to be caused by the study vaccine nrust be reported to GSK or its designee. These SAEs will beprocessed by GSK or its designee as during the course of the study, until 1 month after Last Subject Last Visit (LSLV). Instructions and contact details for collecting and reporting these suspected SAEs will beprovided to the investigato.r

7.1.6 Pregnancies

To ensure subjects' safety, each pregnancy in a subject after study vaccination must be reported to GSK or delegate 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 GSK or delegate. 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, Serious Adverse Events) must also be reported on the VSAE Report Form.

7.1.7 Safety Laboratory Measurements

No safety laboratory measurements will be done in this study.

7.2 Efficacy Assessment

This section is not applicable. This study has no efficacy measurements.

7.3 Immunogenicity Assessment

The functional measure of immunogenicity used in this study, Serum Bactericidal Assay (SBA), is a measure of the ability of antibodies, in concert with human complement, to kill meningococci, and is widely used and generally recognized as the serological correlate of protection The key measures of immunogenicity will be the percentages of subjects with seroresponse[1], percentages of subjects who achieve hSBA titers 8 and, and the hSBA GMfs against serogroups A, C, W and Y reference strains

These measurements will be assessed in serology samples collected at Visit Day 1, 4 or 8 and Day 29. The measures of immunogenicity used in this study are standard, i.e., widely

[1] Seroresponse to N. meningitidis serogroups A, C, W and Y is defined as: for subjects with a pre-vaccination hSBA titer < 4, a post-vaccination hSBA titer 2:8; for subjects with a pre-vaccination hSBA titer 2:4, an increase in hSBA titer of at least four times the pre-vaccination titer.

used and generally recognized as reliable, accurate, and relevant (able to describe the quality and extent of the immune response).

All subjects will have a blood draw at Day I, before vaccination. Subsequent blood draws willbe at either Day 4 or Day 6 post vaccination, and at Day 29 post vaccination.

Primary:

Collected samples may be used in other assays, for test improvement or development of analytical methods related to the study vaccines or the disease under evaluation to allow a more reliable measurement of the vaccine response. Under these circumstances, additional testing on the samples may be performed by GSK outside the scope of the protocol Any sample testing willbe done in line with the consent of the individual subject's parent/ guardian.

Testing willbe conducted by qualified and certified laboratories. All assays will be performed in GSK, Clinical Laboratory Sciences, or a delegate laboratory.

8. STATISTICAL CONSIDERATIONS

8.1 Endpoints

8.1.1 Plimai-y En dpoint(s)

8.1.1.1 Plim ary Safety Endpoint(s)

There are no primary safety endpoints in this study.

8.1.1.2 P1imar y Efficacy Endpoint(s)

There are no primary efficacy endpoints in this study.

8.1.1.3 P1imary Immunogenicity Endpoint(s)

Thefollowing measure willbe summarized for the pooled (Menveo-Menveo and Menactra-Menveo) group

1. Percentage of subjects with hSBA seroresponse[5] against *N. meningitidis* serogroups A, C, W and Y at Day 29.

8.1.2 Secondary Endpoint(s)

8.1.2.1 Secondary Safety Endpoint(s)

Safety of the study vaccine willbe assessed in the pooled vaccine group (Menveo-Menveo and Menactra-Menveo) and the vaccine-naive group in terms of the frequency (percentage) of reported adverse events including

1. Any unsolicited AEs reported within 30 minutes after vaccination;
2. Solicited local and systemic AEs reported from Day 1 (6 hours) through Day 7 after vaccination;
3. Other indicators of reactogenicity (e.g. use of analgesics/ antipyretics, body temperature) within 7 days after vaccination;
4. All unsolicited AEs reported from Day 1 through Day 29 after vaccination;

[5] Seroresponse is defined as: a) post-vaccination hSBA?:8 for subjectswith a pre-vaccination hSBA <4; b) for subjects with a pre-vaccinationhSBA ?:4, an increase of at least four timesthe pre-vaccinationhSBA.

5. Medically-attended AEs, AEs leading to withdrawal and SAEs reported from Day 1 through Day 181 (entire study period).

Adverse events will be coded using MedDRA preferred terms as applicable.

8.1.2.2 Secondary Efficacy Endpoint(s)

There are no secondary efficacy endpoints in this study.

8.1.2.3 Secondary Immunogenicity Endpoint(s)

The following measures will be summarized for Menveo-Menveo, Menactra-Menveo, Naive and the pooled (Menveo-Menveo and Menactra-Menveo) groups unless otherwise noted:

1. Percentage of subjects with hSBA titer ≥8 against *N. meningitidis* serogroups A, C, W and Y at Day 1, Day 4, Day 6 and Day 29;
2. Percentages of subjects with hSBA seroresponse against *N. meningitidis* serogroups A, C, W and Y at Day 4, Day 6 and Day 29 (Day 29: Except the pooled group);
3. hSBA GMTs against N. *meningitidis* serogroup A, C, W and Y at Day 1, Day 4, Day 6 and Day 29;
4. Ratios of hSBA GMTs at Day 1, Day 4, Day 6 and Day 29 (between study groups).
5. Ratios of hSBA GMTs at Day 4, Day 6, and Day 29 compared to Day 1 (within study groups).

8.1.3 Exploratory Endpoint(s)

8.1.3.1 Exploratory Safety Endpoint(s)

There are no exploratory safety endpoints in this study.

8.1.3.2 Exploratory Efficacy Endpoint(s)

There are no exploratory efficacy endpoints in this study.

8.1.3.3 Exploratory Immunogenicity Endpoint(s)

There are no exploratory immunogenicity endpoints in this study.

8.2 Success C1iteria

8.2.1 Success C1iteria for P1imary Objective(s)

82.1.1 Success C1ite1ia for P1imary Safety Objective(s)

There are no primary safety objectives in this study.

82.1.2 S uccess C1ite1ia for P1ima ry Efficacy O bjective(s)

There are no primary efficacy objectives in this study.

82.1.3 Success C1ite1ia for P1imary Immunogenicity Objective(s)

To demonstrate immune response sufficiency after MenACWY-CRM booster vaccine administration, the lower limit of the one-sided 97.S% Confidence Interval(CI) for percentage of subjects with hSBA seroresponse against each of serogroups A, C, W and Y must be greater than 80% (in the pooled group of subjects who received primary vaccination with Menveo or Menactra). The threshold of80% was previously agreed for demonstration of immune response adequacy in other age groups (e.g. in infants, study VS9_36).

8.2.1.3.1 Rationale for Combining the Menveo-Menveo and Menach·a-Menveo groups

Table 8.2.1.3.1-1 shows excerpt of data from a previous study (VS9Pl3El) assessing the immunogenicity of a booster dose of Menveo among subjects who had previously been vaccinated with either Menveo or Menactra 3 years prior in another study (VS9P13) while subjects were 11-18 years old. The table shows almost identical seroreponse rates and 95% Cls at one-month post-booster dose of Menveo for subjects previous vaccinated with Menveo and Menactra. This suggests that data from the two groups can be pooled or combined for analysis of seroresponse following a booster dose of Menveo as planned in the current study VS9_77.

Table8.2.l.3.l-1: hSBASeroresponse at One Month Following the Booster at 3 Years After Vaccination, by Serogroup - Booster- PP Population

Vaccination	ACWY/ACWY Gt·oup IV	MenactJ"a/A Y GroupV	Difference' G1·onpIV - G1·onpV
Overall Seroresponse	68 (97%) (90-100) N=70	70(100°/o) (95 -100) N=70	(-3%) (-10-2)
Overall Seroresponse	*66* (93%) (84-98) N=71	*65* (93%) (84-98) N=70	(0%) (-9-10)
Overall Seroresponse	63 (91%) (82-97) N=69	64 (93%) (84-98) N=69	(-! %) (-11-8)
Overall Seroresponse	63 (90%) (80-96) N=70	*65* (93%) (84-98) N=70	(-3%) (-13-7)

Source: Table14.2.1.7ofClinicalStudyReportforV59Pl3El;'Datarepresentedas(differencein%)(95% CI ofdifference).

8.2.2 Success C1iteria for Secondary Objective(s)

8.2.2.1 Success C1ite1ia for Secondar y Safety Objective(s)

There are no success criteria associated with the secondary safety objectives.

8.2.2.2 Success C1ite1ia for Secondar y Efficacy Objective(s)

There are no secondary efficacy objectives in this study.

8.2.2.3 Success C1ite1ia for Secondary Immunogenicity Objective(s)

There are no success criteria associated with the secondary immunogenicity objectives in this study.

8.3 Analysis Sets

8.3.1 AllEnrolled 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 enrolied set who receive a study vaccination.

8.3.3 Safety Set

Solicited Safety Set (solicited local and systemic adverse events and other solicited adverse events)

All subjects in the Exposed Set with any solicited adverse event data.

Unsolicited Safety Set (unsolicited adverse events)

All subjects in the Exposed Set with unsolicited adverse event data.

Overall Safety Set

All subjects who are in the Solicited Safety Set and/or Unsolicited SafetySet.

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 AnalysisSet (FAS)Efficacy/lmmunogenicity Set

Full Analysis Set Immunogenicity

FAS <Day 1)

All subjects in the All Enrolled Set who:

- are randomized;

- provide evaluable serum samples at Day 1 whose result is available for at least one serogroup.

FAS (Day4)

All subjects in the All Enrolled Set who:

- are randomized;
- receive the study vaccination;
- provide evaluable serum samples at Day 1 whose result is available for at least one serogroup (except for hSBA titer 8, GMTs and between-group GMRs calculated at specific timepoints); and
- provide evaluable serum samples at Day 4 whose result is available for at least one serogroup.

FAS(Day6)

All subjects in the All Enrolled Set who:

- are randomized;
- receive the study vaccination;
- provide evaluable serum samples at Day 1 whose result is available for at least one serogroup (except for hSBA titer 8, GMTs and between-group GMRs calculated at specific timepoints);
- provide evaluable serum samples at Day 6 whose result is available for at least one serogroup.

FAS (Day29)

All subjects in the All Enrolled Set who:

- are randomized;
- receive the study vaccination;
- provide evaluable serum samples at Day 1 whose result is available for at least one serogroup (except for hSBA titer 8, GMTs and between-group GMRs calculated at specific timepoints);
- provide evaluable serum samples at Day 29 whose result is available for at least one serogroup.

In case of vaccination error, subjects in the 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.S Per Protocol (PP) Set Efficacy/Immunogenicity Set

A PPS will be defined for each FAS described in the previous Section with additional criteria specified below:_All subjects in the FAS Immunogenicitywho:

- Correctly receive the study vaccine (i.e., receive the vaccine to which the subjects is randomized and at the scheduled time points).
- Have no protocol deviations leadingto exclusion (see section 8.3.8, Protocol Deviations) as defined prior to unblinding / analysis.
- Are not excluded due to other reasons defmed prior to unblinding or analysis (see section 8.3.8, Protocol Deviations)

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

Subjects who withdrew informed consent.

8.3.6 Other Analysis Sets

There are no other analysis sets used in this study.

8.3.7 Subgroups

Using the FAS (Day 29), the analyses of the primary objectives will be replicatedby: age group; center; gender; and race.

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. CSR-reportable protocol deviations will be defined as exclusionary fromthe 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. earlytermination.

8.4 Statistical Analysis Plan

8.4.1 Analysis of Demographic and Baseline Characteristics

Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age, height and weight at enrolment will be calculated overall and by study group.

Distributions of subjects by sex and ethnic origin will be summarized overall and by study group.

8.4.2 Analysis of Primary Objective(s)

8.4.2.1 Analysis of Primary Safety Objective(s)

There are no primary safety objectivesin this study.

8.4.2.2 Analysis of Primary Efficacy Objective(s)

There are no primary efficacy objectives in this study.

8.4.2.3 Analysis of Primary Immunogenicity Objective(s)

8.4.2.3.1 Statistical Hypotheses

Null hypothesis: $P_i \leq 0.80$

versus

Alternative hypothesis: $P_i > 0.80$

Where: P_i is the population seroresponse rate for the pooled Menveo-Menveo and Menactra-Menveo group; $i = 1, 2, 3, 4$ refer to serogroup A, C, W and Y respectively. The level of significance is fixed at one-sided 0.025.

8.4.2.3.2 Analysis Sets

The analysis population to be used for the primary objectives is the FAS (Month 1) Set. Analyses of primary objectives will be repeated on the PPS (Month 1) to assess robustness of results.

8.4.2.3.3 Statistical Methods

General

Missing immunogenicity values are assumed MCAR (Missing Completely At Random) and therefore may not contain information that impact the result of the analysis (i.e., not informative). Imputation methods will therefore not be used.

Overall significance level for all hypothesis tests is one-sided $\alpha = 2.5\%$.

Seroresponse (Day 29)

Seroresponse is defined as: a) post-vaccination hSBA titer 8 forsubjects with a pre-vaccination hSBA titer <4; b) forsubjects with a pre-vaccinationhSBA titer 4, an increase of at least four times the pre-vaccination hSBA.

For each ACWY serogroup, the percentage of subjects withseroresponse willbe computed, along with associated two-sided 95%Clopper-Pearson Cls.

Further details of the statistical methods will be provided in the SAP.

8.4.3 Analysis of Secondary Objective(s)

8.4.3.1 Analysis of Secondary Safety Objective(s)

8.4.3.1.1 Analysis of Extent of Exposure

Subjects will be analyzed to the extent that they were exposed to study vaccines and according to the available safety data for the subject during any study period. Subjects who withdraw early or who are lost to follow-upwill be removed from the summary table denominator for the time period in which they have no available safety data collected.

8.4.3.1.2 Analysis of Solicited Local, Systemic an d Oth er AdverseEvents

All solicited adverse events will be summarized according to defined severity grading scales.

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

Post-vaccinationsolicited adverse events reported from Day 1 to Day 7 willbe summarized for the intervals Day 1 (6 hours) - Day 3, Days 4-7, Day 1 (6 hours) - Day 7 by maximal severity and by study group. Separate analyses will be performed for solicited AEs reported 30 minutes after vaccination. Theseverity of solicited local adverse events, including injection-site erythema and induration, will be categorized based on linear measurement: None (0-24 mm), Mild (25-50 mm), Moderate (51-100 mm), Severe (> 100mm).

Injection site pain and systemic reactions, including fatigue, headache, myalgia, arthralgia, chills, nausea, lossof appetite, occurring up to 7 days after each vaccination 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'.

Use of antipyretics and analgesics will be summarized by frequency, by type of use (prophylactic versus treatment) and percentage of subjects reporting use.

Body teJl1)erature will be summarized separately according to the 3 schemes described below and will be broken down according to route of measurement:

- by O.S °C increments from 36.0°Cup to ,::40°C;
- by 1°C increments: <36.0, 36.0-36.9, 37.0-37.9, 38.0-38.9, 39.0-39.9, ,::40°C;
- According to different cut-offs (< versus ::::): 38 .0, 38 .S, 39 .0, 39 .S, 40 .0 °C .

8.4 .3 .1. 3 An al ys i s o f U n so li cited Advene Events

1bis 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 dateof first vaccination. AE starting prior to the first vaccination willonly 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 (SOC).

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 SOC and preferred term within SOC. These summaries will be presented by study group 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 will be counted.

Separate summaries will be produced for the following categories:

- Adverse events that are possibly or probably related to vaccine
- Unsolicited AEs reported within 30 minutes after vaccination
- Unsolicited AEs reported within 30 days after vaccination
- Adverse events leading to withdrawal
- Adverse events leading to a medically attended visit
- Serious adverse events

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.

8.4.3.1.4 StatisticalHypotheses

There are no statistical hypotheses associated with the secondary safety objectives.

8.4.3.1.S Analysis Sets

Analyses of solicited adverse events - and other solicited reactions - and unsolicited adverse events will be performed on the relevant safety sets.

8.4.3.1.6 StatisticalMethods

For unsolicited adverse events, the entirestudy period will be divided into the following intervals: onset within30 minutes after vaccination , onset within 28 days after vaccination; and from Day 1 through Day 181. For solicited adverse events, the solicited study period will be divided into intervals: from 6 hours through day 3; from day 4 through day 7; and from 6 hours through day 7.

No imputation methods will be used to address missing safety data.

Snmmarif>s of safety will be presented using frequencies and percentages within each study group. No statistical comparisons among the studygroups with respect to any of the safety parameters will be performed.

8.4.3.2 Analysis of Secondary Efficacy Objective(s)

There are no secondary efficacy objectives associated with this study.

8.4.3.3 Analysis of Secondary Immunogenicity Objective(s)

8.4.3.3.1 Sta tistical Hypotheses

Analyses related to the secondary immunogenicityobjectives will be descriptive; no formal statistical tests will be performed.

8.4.3.3.2 Analysis Sets

Analyses of secondary imm1mogenicity will be based on the FAS and repeated on the PPS.

8.4.3.3.3 Statistical Methods

General

The hSBA titers at each visit will be logarithmicallytransformed (baselO) to obtain approximately nonnally distributed data.

For comparison of percentages and GMT ratios, unadjusted estimates will be obtained along with adjusted estimates from regression models to account for potential baseline imbalance between study groups.

For each *N. meningitidis* serogroup A, C, Wand Y, unadjusted GMTs will be calculated, withtheir associated two-sided 95% Cls, by exponentiating the corresponding log-transformed means and their 95% Cls. Adjusted GMR.s will be obtained from Analysis of Covariance (ANCOVA) models.

See section 8.4.2.3.3 for other relevant details.

Seroresponse (Day 29)

The percentage of subjects with seroresponse and associated two-sided 95% Clopper-Pearson Cls will be computed by group (Menveo-Menveo, Menactra-Menveo, and Naive) and *N. meningitidis* serogroups **A,** C, W and Y teststrains. Differences in percentages and associated 95% Cls between study groups will be calculated using the Miettinen & Nurminen score method.

In a descriptive fushion - using the difference in percentages and 95% Cls - each of the previously vaccinated groups will be compared to the nai:ve group . Also the two previously vaccinated study groups will be compared to each other.

As sensitivity analyses, the difference in percentages will also be obtained from a log-linear model adjusting for center, pre-vaccinationtiter and age-group. Please see SAP for technical details.

Percentage of Subjects \Vith hSBA titere::8 (Da y I, Da y 4, Da y 6, and Da y 29)

For each study group and in the pooled group, the percentage of subjects with hSBA titer 8 andassociatedtwo-sided 95% Clopper-Pearson Cls will be computed by the *N. meningitidis* serogroups A, C, W and Y teststrains on Day 1, Day 4, Day 6 and Day 29 (as applicable, depending on blood draw schedule).

Differences in percentages and associated 95% Cls between study groups will be calculated using the Miettinen & Nurminen score method.

In a descriptive fashion - using the difference in percentages and 95% Cls - the previously vaccinated groups (individually and pooled) will be compared to the naive group. Also the two previously vaccinated groups will be compared to each other.

As sensitivity analyses, the difference in percentages will also be obtained from a log-linear model adjusting for center, pre-vaccinationtiter and age-group. Please see SAP for technical details.

Between-group Ratios of Gl\\lT s (A d jus ted and U nad ju sted)

The between -group ratio ofhSBA GMTs and corresponding 95% CI, at each of Visit Day 1 (Persistence), Day 4, Day 6 and Day 29 against each *N. meningiti.dis* serogroups A, C, W and Y test strains will be obtained by exponentiatingthe mean between-group differences in log-transformed titers and the corresponding 95% Cls at each of the timepoints specified.

Additionally, adjusted ratio of GMTs will be obtained fromANCOVA models including center, pre-vaccination titer and age-group as factors in the model.

The previously vaccinated groups (individually and pooled) will be compared to the naive group at each timepoint - descriptively - using the ratios of GMTs.

The two previously vaccinated groups will be compared at each timepoint using GMT ratios.

\Within-gro up Ratios of Gl\\lT s (Ad jus ted an d U na d ju sted)

Within each study group and for each antigen/serotype, ratios of GMT will be calculated, as applicable, at:

- Visit Day 4 versus at Visit Day 1;
- Visit Day 6 versus at Visit Day 1; and
- Visit Day 29 versus at Visit Day 1.

The unadjusted GMRs and 95% Cis will be constructed by exponentiating the mean within-groupdifferences in log-transformed titers and the corresponding 95% Cls.

Adjusted GMRs will be obtained from Analysis of Covariance (ANCOVA) models including center and age-group as factors in the model.

Further details of the statistical methods will be provided in the Statistical Analysis Plan (SAP).

8.4.4 Analysis of Exploratory Objectives

8.4.4.1 Analysis of Exploratory Safety Objective(s)

There are no exploratory safety objectives in this study.

8.4.4.2 Analysis of Exploratory Efficacy Objective(s)

There are no exploratory efficacy objectives in this study.

8.4.4.3 Analysis of Exploratory Immunogeoicity Objective(s)

There are no exploratory immunogenicityobjectives in this study.

8.5 Sample Size and Power Considerations of Ptimary Objectives

Statistical power was estimated based on observed data from study V59Pl3El, where seroresponse rates at one-monthpost booster dose of MenACWY-CRM ranged from 97% (90%-100%) to 100% (95%-100%)for serogroup A, 93% (85%-98%) for serotype C; 91% (82%-97%) to 93% (84%-98%) for serogroup W; and 90% (80%-96%) to 93% (84%-98%) for serogroup Y among subjects printed with MenACWY-CRM or Menactra in the three years preceding the study.

Assuming the true seroresponse rates in the pooled group range from 90% to 97% (alternative hypothesis) for each serotype, a sample size of n=540will have at least 96% power to show sufficiency of immune response to a booster dose of MenACWY-CRM in the pooled group, compared with a pre-specified reference seroresponse of 80% (null hypothesis) using an exact test with 0.025 one-sided significance level. When taking a 10% dropout rate into account, N=600 previously vaccinated subjects have to be enrolled in the study. Calculations have been done with nQuery Advisor (Version 7.0).

Table 8.5-1: Statistical Power to Test for Sufficiency of Immune Response Given a Range of True Sero response Rates for Evaluable Sample Size of 540 subjects

Ser ot}11e	T111e Seroresponse Rate	Power
A	0.97	0.99
C	0.93	0.99
W	0.91	0.99
y	0.90	0.99
Total Power		0.96

8.6 Interim Analysis

No interim analysis of data from this studyis planned.

9. SOURCE DOCUMENTATION, STUDY MONITORING AND AUDITING

In order to ensure consistency across sites, 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 willtrain investigators and/or their study staff on the study protoco allapplicable studyprocedures, documentation practices and all electronic systems. CRFs supplied by the Sponsor must be completed for each randomized subject (see section 8.3.1, All Enrolled Set 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 willbechecked 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 willberequired for review as source documents. The kinds of documents that willserve as source documents willbe 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/or parent(s)/legal guardian(s) and date of completion and reason.

The subject and/or parent(s)/legal guardian(s) must also allow access to the subject's medical records. Each subject and/or the parent(s)/legal guardian(s) 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 safetydata 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, thesesources 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 infonnation were used to detennine the adverse event (e.g., subject recall, medical chart, Subject Diary).

9.2 Study Monit01ing, Auditin g a nd So urce Data Verification

Prior to enrolment of the first study subject, GSK or its designee (e.g., a CRO) will develop a Clinical Monitoring Plan to specify how centralized and/or on-site monitoring, including clinical specimens reconciliation, will be perfonned for the study. Study progress will be monitored by GSK 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 cUITent approved protocol/amendment(s), GCP and applicable regulatory requirements.

Contact details for the GSK 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. .

Data verification may also be performed through a centralized review of data (e.g., checking for outliers or other anomalies). Additional documents such as the investigator site file, phannacy records, and infonned 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 GSK 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 regulation,sby 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 infonnation related to the study and enrolled subjects.

10. DATA MANAGEME1"T

10.1 Data Entry and Management

In this study, all clinical data (including, but not limited to, AF/SAEs, concomitant medications, medical history, and physical assessments), safety data, and immllllogenicity data will be entered onto case report forms (CRFs) in a timely fashion by the investigator and/or the investigator 's dedicated site staff. Data entered onto CRFs are stored on a secure website. The data collected on this secure website are assimilated into an electronic data capture (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 nrust review data entered and electronicallysign the CRFs to verifytheir accuracy.

Access to the EDC system for data entryor 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.

10.2 Data Cla1ifi cation

As part of the conduct of the trial, the Sponsor may havequestions 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 willensure the confidentiality of their medical information in accordance with all applicablelaws and regulations.

11. 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 representativebefore disposal of any studyrecords, andmust notify the Sponsor of any change in the location, disposition, or custody of the study files. Essential documents must be retained for 1S years. "Essential documents" are defined as documents that individually and collectively pennit 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 immtmogenicity samples, provided that the integrity of the stored sample pennits testing.

12. USE OF JIl,'FORMATION AND PUBLICATION

GSK assures that the key design elements of this protocol willbe posted in a publicly accessible database such as clinicaltrials.gov, and in compliance with ct11Tent 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 theend of study as defined in section 3.9, End of Study.

In accordance withstandard editorial, ethical practices and ct11Tent guidelines of Good Publication Practice (Graf2009), GSK will generally support publication ofmulticenter studies only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement prior to the start of the study. The coordinating investigator will also sign the clinical study report on behalf of the principal investigators (CPMP/EWP/2747/00). Authorship willbe determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any fonnal publication of the studyin which contribution of GSK personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate GSK personnel.

Novartis 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. ETIDCAL CONSIDERATIONS

13.1 Regulatory and Ethical Compliance

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

This clinical study was designed and shall be implemented and reported in accordance withthe ICH HarmonizedTripartite Guidelines for GoodClinical Practice, with applicable local regulations including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry ofHealth, Labor, and Welfare, GSK codes on protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki(EuropeanCouncil 2001, US Code of Federal Regulations, ICH 1997).

13.2 Informed Consent Procedures

Eligiblesubjects may only be included in the study after providing written informed consent or assent, as described in section 5.1.1, Informed Consent/Assent. Before the start of the study, the investigatorwill have the informed consent and any other materials that will be provided to the subjects reviewed and approved bythe IRB/EC. This review and approval will bedocumented andstored withother studydocuments. The investigator or designee must fully inform thesubject 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. Thesubject/designeemust be allowed ample time to ask about thedetails 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 theconsent form indicating their agreement to participate in the studybefore anystudy-related procedures are conducted. The informed consent process may be conducted up to *5* days prior to vaccination on Day I. If the subject and/or legal guardian(s) 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 byGSK before submission to the IRB/EC and a copy of the approved version must be provided to the GSK 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. If case of doubts on the ability of a subject to adhere to these requirements, that subject should not be allowed in the study

Before the start of the study, the investigator will have the informed assent, the informed consent, and any other materials that will be provided to the subject and/or parent(s)/legal guardian(s) 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 and/or parent(s)/legal guardian(s) of all pertinent aspects of the study. A copy of the written informed consent and informed assent will be given to the subject and/or parent(s)/legal guardian(s).

In addition, the investigator or designee should explain pertinent aspects of the study in an age appropriate manner to pediatric subjects who are eligible for informed assent in accordance with local policies. The subject and parent(s)/legal guardian(s) 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 parent(s)/legal guardian(s) must sign the consent/assent forms indicating their agreement to participate in the study before any study-related procedures are conducted. If the subject and/or parent(s)/legal guardian(s) are unable to read and write, a witness must be present during the informed consent/assent discussion and at the time of informed consent/assent signature.

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 (RI), 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 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 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 protoco the investigationalproduct(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 and/or parent(s)/legal guardian(s), 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 theIRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when thechange(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone nwnber(s)). In addition, the investigato,ror person designated by the investigato,rshould 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 theIRB/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 protocolwhich 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, samplesizes, studyprocedures, 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 nrust 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 amendmen,t the investigator is expected to take any inunediate 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. REFERENCE LIST

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Novartis

Document A !J!roval Ce rtificate /

PPD

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The indivi:luals listed have appl'()ved this document for ii!Jplementation using an electronic si ture in the Atlas EDMS. PPD

U serName:pp-o• - - - .. PP D

Ti tle: Cluster Phys ician -Meningi tis an d Sepsis Franchise

Date: Friday, 12 February 20 16 , 09:32 GMT

Meaning: As an approver, I agree with the content and format of this document

CLINICALSTUDY PROTOCOL VS9 77 **Version** 3

A Phase 3b, Controlled, Open-Label, Multi-Center Studyto Evaluate Safety and Inumnogenicity of a Single Dose of GlaxoSmithKline's Meningococcal ACWY Conjugate Vaccine (Menveo), Administered to Healthy Individuals 15 through 55 years of age, approximately 4-6 years after primary ACWY vaccination.

Safety and Immunogenicity Study of a Single Dose of Menveo, Administered to Subjects 15 through 55 years of age, approximately 4-6 years after primary ACWY vaccination

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PR OTO COL SYNOPSIS V59 77

Name of Sponsor:	**Protocol number:**	**Gene1ic name of study vaccine(s):**
GlaxoSmithKline Vaccines	V59 77	Meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine

Title of Study: A Phase 3b, Controlled, Open-Label, Multi-Center Study to Evaluate Safety and Immunogenicity of a Single Dose of GlaxoSmithKline's Meningococcal ACWY Conjugate Vaccine (Menveo), Administered to Healthy Individuals 15 through *55* years of age, approximately 4-6 years after primary ACWY vaccination.

Study **Pe1iod:** Approximately 180 days (six months).	**Clinical Phase:** 3b

Background and Rationale:

Neisseria meningitidis is a leading cause of bacterial meningitis and sepsis worldwide, capable of causing outbreaks and epidemics of invasive disease. Meningococcal disease is associated with high morbidity and mortality even among patients who receive early antibiotic treatment. Most cases of invasive disease worldwide are caused by serogroups A, B, C, W and Y.

The quadrivalent meningococcal oligosaccharide diphtheria CRM-197 conjugate vaccine (MenACWY-CRM; Menveo, GSK Vaccines) is approved for active immunization of individuals from 2 months through *55* years of age in the United States. As of February 2015, more than 30,000 of subjects have been exposed to MenACWY-CRM vaccine in completed clinical studies and more than 24 million doses of the vaccine have been distributed globally

The US Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination with a quadrivalent conjugated meningococcal vaccine for adolescents at 11-12 years of age with a booster dose administered *5* years later. While a substantial body of data exists showing a robust immune response and good antibody persistence after a single dose of MenACWY-CRM in adolescents, the response to a booster dose of MenACWY-CRM in this age group has only been evaluated in 2 clinical studies with limited number of subjects.

A robust anamoestic immune response to a booster dose of Menveo vaccine administered at approximately *5* years after previous vaccination with the same vaccine or a licensed meningococcal oolysaccharide vaccine (Menomune®) was demonstrated in

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the phase 2 clinical study V59P6El . High titers of bactericidal antibodies against the vaccine serogroups were achieved at 7 and 30 days after booster dose in MenACWY-primed subjects. However, the number of subjects included in this study was relatively small (N=101, including 50 subjects who received a booster dose after the primary MenACWY-CRM vaccination).

In the phase 3b clinical study V59Pl3 El , a booster dose of MenACWY-CRM was given 3 years after primary vaccination with either MenACWY-CRM or Menactra®(a meningococcal diphtheria toxoid-conjugated MenACWY vaccine, MenACWY-D) in adolescents.A booster dose was able to substantially increase antibody titers against all 4 serogroups irrespective of the priming vaccine. Again, only a small number of subjects (N=160) received the MenACWY-CRM booster, (83 who received primary MenACWY-CRM and 77 who received MenACWY-D).

In the light of thecurrent ACIP recommendation for a booster dose of MenACWY-CRM, there exists a need to evaluate the response to a MenACWY-CRM booster given at -5 years after primary vaccination in meningococcał vaccine primed adolescents. Generation of this data would also be of relevance in outbreak management and vaccination of travelers to endemic areas.

The purpose/aim of this study is to assess the safety and antibodyresponse to vaccination with a booster dose of Menveo given 4-6 years after primary vaccination and the response to a single dose given to vaccine-naive subjects, and to describe the immune response over time after a single dose of Menveo, administered to subjects previously vaccinated with Menveo or Menactra or to vaccine-naive subjects. The inclusion of vaccine-naive subjects in a separate study arm is to enable comparison of the rapidity and magnitude of an aoarooestic response to a booster dose (in primed individuals) or the primary response to a first dose (in naive individuals) of MenACWY-CRM.

Study Objectives:

P1i mary Objective(s): Immunogenicity objective:

L To demonstrate a sufficient immune response following a single dose of MenACWY-CRM(Menveo) vaccine, !riven to subjects who previously received

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Menveo or Menactra, as measured by the percentage of subjects with hSBA seroresponse against *N. meningitidis* serogroups A, C, W and Y at Day 29 after vaccination

Criteria to demonstrate immune response sufficiency: The immune response will be considered as sufficient if the lower limit of the one-sided 97.5% CI for percentage of subjects with hSBA seroresponse against serogroups A, C, W and Y is greater than 80% (zn pooled group of subjects who received primary vaccination with Menveo or Menactra).

Seco ndary O bjec tive(s) :

Immunogenicity objectives:

1. To compare the immunogenicityofa single dose ofMenACWY-CRM vaccine, between subjects who previously received Menveo, subjects who previously received Menactra and vaccine-naive individuals, as measured by the percentage of subjects with hSBA titer 8, withhSBA seroresponse, and hSBA GMTs against *N. meningitidis* serogroups A, C, W and Y at Day 29 after vaccination
2. To compare the immune responses over time following a single dose of MenACWY-CRM vaccine, between subjects who previously received Menveo, subjects who previously received Menactra and vaccine-naive individuals, as measured by the percentage of subjects with hSBA titer ,::8 and hSBA GMTs against *N. meningitidis* serogroups A, C, Wand Y at Day I, Day 4, Day 6, and Day 29 after vaccination
3. To assess persistence of bactericidal antibodies against serogroups A, C, Wand Y at approximately 4-6 years after the primary vaccination with Menveo and after the primary vaccination with Menactra in comparison with naturally-acquired level in vaccine-naive individuals, as measured by the percentage of subjects with hSBA titer ,::8 and hSBA GMTs at Day 1.

Safety objectives:

1. To assess reactogenicity and safety of MenACWY-CRM vaccine when administered to subjects who previously received Menveo or Menactra and vaccine-naive individuals

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
GlaxoSmithKline Vaccines	V59 77	Meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine

Study Design:

This is a phase 3b, controlled, open-label, multi-center study to evaluate safety and immunogenicity of MenACWY-CRM after a single vaccination in healthy individuals who were vaccinated with Menveo or Menactra 4 to 6 years ago and in vaccine-naive individuals.

Study population: Approximately 700 healthy subjects 15 through 55 years of age will be enrolled in the study.

Duration of the study: The duration of this study is approximately 6 months per subject.

Written informed consent and, as applicable according to local guidelines, written assent will be obtained before conducting any study-specific procedures.

Vaccination schedule: All subjects will receive a single dose of MenACWY-CRM at Day 1.

Study groups:

- Group Menveo-Menveo: approximately 300 subjects, who were vaccinated with a single dose of Menveo 4 to 6 years ago, will receive one dose of MenACWY-CRM.
- Group Menactra-Menveo: approximately 300 subjects, who were vaccinated with a single dose of Menactra 4 to 6 years ago, will receive one dose of MenACWY-CRM.
- Group Naive: approximately 100 subjects, of similar age to subjects enrolled in other primed groups, equally enrolled across all clinical sites, who have not received any meningococcal vaccination, will receive one dose of MenACWY-CRM.

Randomization/ Stratification:

Within each study group, subjects will be randomized into one of two different blood draw schedules according to a 1:1 ratio, described as follows:

- Subjects getting blood draws at Day 1, Day 4 and Day 29.
- Subjects getting blood draws at Day 1, Day 6 and Day 29.

Name of Sponsor:	Protocol number:	Gene1i c name of study vaccine(s):
GlaxoSmithKline Vaccines	V59 77	Meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine

For a schematic overview, see Table 1.

Ta ble I: Schema tic diagra m of the VS9_77 stu dy gro ups

Vacc.ine History	Vacc.ination in current study	Blood drawschedule
Menveo N=300	Menveo	Blood draw Day 1, 4, 29 (N=l50)
		Blood draw Day **1,** 6, 29 (N=l50)
Menactra N=300	Menveo	Blood draw Day 1, 4, 29 (N=l50)
		Blood draw Day **1,** 6, 29 (N=l50)
Vaccine-Naive N=IOO	Menveo	Blooddraw Day I, 4, 29(N=50)
		Blooddraw Day I, 6, 29(N=50)

Blinding: open-label study.

Blood samn!P.s: Three (3) blood samples of approximately 10 mL each willbe collected according to the blood draw schedule in Table I.

Data collection: Electronic Case Reporting Form (eCRF).

Study clinic visits: Three (3) clinic visits at Day 1, Day 4 or Day 6 and Day 29 are piaruied for eachsubject.

Reminder Phone calls: Two (2) reminder phone calls will beconducted at Day 3 and Day *5* after the study vaccination to remind the subject/ legal guardian to complete the diary card.

Safety phone calls: Three (3) safety phone calls (at Day 15, Day91 and Day181) will be conducted to collect any medically-attended AEs, AEs leading to withdrawal, SAEs, related medications and any vaccinations. In addition, all unsolicited AEs and related medications occurring after the vaccination willbe collected during the safety call at Day15.The Day 181 Safety Phone call will also serve as the termination visit.

Solicited Adverse Events (injection site pain, erythema, induration, fatigue, headache, myalgia, arthralgia, loss of appetite, nausea, chills and fever) occurring on the day of vaccination and the following six davs ffiav I throu h Dav7) will be recorded daily

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using a Diary Card for all subjects.

Unsolicited AEs occurring within 28 days after studyvaccination willbecollecte.d Qualified site staff willinterview the subject by phone approximately 14 days after vaccination and in person at the study site approximately 28 days after study vaccination to assess the occurrence of any unsolicited AEs.

Medicall}'.-attended AEs AEs leading to stud}'.withdrawal and SAEs will be collected during the entire study period. These data will becaptured by interviewing the subject and/or subjects' parents / guardian (as applicable) during the site visits and phone calls and by review of available medical records. Subjects and/or parents / guardian willbe encouraged to call the site in the event of any medically-attended AEs or any AEs which theyperceive as being of concern during the entire studyperiod.

Table 2: Schematic diagram of the VS9_77 study design.

Day l	Day 4	Day 6	Day15	Day 29	Day 91	Day 181
Blood draw (all subjects) Menveo	Blood draw (50% of subjects)	Blood draw (50% of subjects)	Safety Phone call	Blood draw (allsubjects)	Safety Phone call	Safety Phone call Study tennination

Number of Subjects planned: Approximately 700 subjects are planned for enrollment into this study, approximately 300 subjects who previously received Menveo (Menveo-Menveo group), 300 subjects who previously received Menactra (Menactra-Menveo group) and 100 meningococcal vaccine-naive subjects (Naive group). Assuming a 10% drop-out rate that should provide approximately 630 evaluable subjects.

Study Populati on and Su bject Char acte1istics: The list of inclusion and exclusion criteria is included in protocol section 4, Selection of Study Population.

Study Procedures: The study includes three clinic visits, one vaccination, three blood draws, and threesafety phone calls for each subject. All studyprocedures associated with the pre-vaccination, vaccination, post-vaccination, unscheduled and study termination visit are described in section 5.0.

Study Vaccines:

Name of Sponsor:	Protocol number:	Gene1i c name of study vaccine(s):
GlaxoSmithKline Vaccines	V59 77	Meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine

GlaxoSmithKline Meningococcal MenAC\1VY - CRl "\1 vacc in e (M en veo): Meningococcal (groups A, C, Wand Y)oligosaccharide diphtheria CRM-197 conjugate vaccine is supplied as a vial contain 10 µg of serogroup A oligosaccharides and 5 µg of serogroups C, W and Y oligosaccharides, conjugated to *Corynebacterium diphtheriae* CRM191 protein. Overall injection volume of 0.5 mL.

The vaccine will be administered intramuscularly, preferably in the deltoid area of the non-dominant arm.

P1i mary Endpoint(s):

Immunogenicity Endpoints:

The following measures will be summarized for the pooled (Menveo-Menveo and Menactra-Menveo) group.

1. Percentage of subjects with hSBA seroresponse[1] against *N. meningitidis* serogroups A, C, Wand Y at Day29.

SecondaryEndpoints:

Immunogenicity endpoints:

The following measures will be summarized for Menveo-Menveo, Menactra-Menveo, Naive and the pooled (Menveo-Menveo and Menactra-Menveo) groups unless otherwise noted:

1. Percentage of subjects with hSBA titer 8 against *N. meningitidis* serogroups A, C, Wand Y at Day 1, Day 4, Day 6 and Day 29;
2. Percentages of subjects with hSBA seroresoonse against *N. meninf!itidis* sero!!I'ouos

[1] Seroresponse is defined as: a) post-vaccination hSBA 8 for subjectswitha pre-vaccination hSBA <4; b) for subjects with a pre-vaccinationhSBA ' an increase of at least four timesthe pre-vaccinationhSBA.

Name of Sponsor:	Protocol number:	Gene1i c name of study vaccine(s):
GlaxoSmithKline Vaccines	V59 77	Meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine

A, C, Wand Y at Day4, Day 6 and Day 29 (Day 29 Except the pooled group);

3. hSBAGMfs againstN. *meningitidis* serogroupA, C, Wand YatDay 1, Day4, Day 6 andDay29;
4. Ratios ofhSBA GMTs at Day 1, Day 4, Day 6 and Day29 (between study groups).
5. Ratios ofhSBA GMfs at Day 4, Day 6, and Day 29 compared to Day 1 (within study groups).

Safety endpoints:

Safety of the study vaccine will be assessed in the pooled vaccine group (Menveo-Menveo and Menactra-Menveo) and the vaccine-naive group in terms of the frequency (percentage) of reported adverse events including:

1. Any unsolicited AEs reported within 30 minutes after vaccination;
2. Solicited local and systemic AEs reported from Day 1 (6 hours) through Day 7 after vaccination;
3. Other indicators of reactogenicity(e.g. use of analgesics / antipyretics, body temperature) within 7 days after vaccination;
4. All unsolicited AEs reported from Day 1 through Day 29 after vaccination;
5. Medically-attended AEs, AEs leading to withdrawal and SAEs reported from Day 1 through Day 181 (during the entire studyperiod).

Statistical Analyses:

P1i mary Immunogenicity Objective

The primary population for the analysis of sufficient immune response is the Full Analysis Set (FAS), and will consist of pooled data from the Menveo-Menveoand Menactra-Menveo group (n=540 evaluable).

To demonstrate immune response sufficiency after MenACWY-CRM booster vaccine administration, the lower limit of the one-sided 97.5% Confidence Interval (CI) for percentage of subjects with hSBA seroresponse against eaciI of serogroups A, C, W and Y must be !!reater than 80% (in the pooled !!!'OUP of subjects who received

Name of Sponsor:	Protocol number:	Gene1ic name of study vaccine(s):
GlaxoSmithKline Vaccines	V59_ 77	Meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine

vaccination with Menveo or Menactra)

Hypothesis:

Null hypothesis — Alternative hypothesis

$P_i \leq 0.80$ — $P_i > 0.80$

Where: P_i is the population seroresponse rate for the pooled Menveo-Menveo and Menactra-Menveo group; i = 1,2,3,4 refer to serotypes A, C, W and Y respectively.

Sample Size:

Statistical power was estimated based on observed data from study V59P13E1, where seroresponse rates at one-month post booster dose of MenACWY-CRM ranged from: 97% (90%-100%) to 100% (95%-100%) for serogroup A; 93% (85%-98%) for serogroup C; 91% (82%-97%) to 93% (84%-98%) for serogroup W; and 90% (80%-96%) to 93% (84%-98%) for serogroup Y among subjects primed with MenACWY-CRM or Menactra in the three years preceding the study.

Assuming the true seroresponse rates in the pooled group range from 90% to 97% (alternative hypothesis) for each serotype, a sample size of n=540 will have at least 96% power to show sufficiency of immune response to a booster dose of MenACWY-CRM in the pooled group, compared with a pre-specified reference seroresponse of 80% (null hypothesis) using an exact test with 0.025 one-sided significance level When taking a 10% dropout rate into account, N=600 previously vaccinated subjects have to be enrolled in the study. Calculations have been done with nQuery Advisor (Version 7.0).

Table 3: Statistical Power to Test for Sufficiency of Immune Response Given a Range of True Seroreponse Rates for Evaluable Sample Size of 540 subjects

Serotype	T111e Serores po nse Rate	**Powel'**
A	0.97	0.99
C	0.93	0.99
W	0.91	0.99

Name of Sponsor:	**Protocol number:**	**Gene1i c name of study vaccine(s):**
GlaxoSmithKline Vaccines	V59_ 77	Meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine

y	0.90	0.99
Total Power		0.96

Interim Analysis: No interim analysis is planned for this study.

Data Monito1i ng Committee: No DMC will be utilized for the study.

Table 4 Time and Events Table

Visit Type		Clinic Visit	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Phone Call
Study period		Screening	Treatment	Tre.itment	Treatment	**Treatment**	Treatment	Follow-up	Followup
Study Day			1	3, 5	4/6•	15	29	91	181
Visit Window (Days)		-5 to 1	0	2 days (-1/+1), 4 da ys (0/+2) after vacc	3/5 days (-1/+1) after vacc	14 days (-2/+2) after vacc	28days (-7/+14) after vacc	90days (-14/+14) **aftel' vacc**	180 days (-14/+14) after vacc
Visit Number		Pre-**vacc.ination**	1	N/A	2	3	4	5	*6*
Study Event	References								
Study Treatment									
Vaccination (vacc)	Section 5.2		X						
Screening **and** Safety									
Informed Consent"	Section 5.1.1	X							
Medical History	Section *5*.1.2	X							
Physical Exam	Sections *5*.1.2 and 5 .3.1	X	X<		X		X		
Pregnancy Test	Sections 3.5 and 5 .1.2	X	X<						
Exclusion/Inclusion Criteria	Section4	X							
Randomization	Section 5.1.4		X<						
30 Minutes Post InjectionAssessment	Section *5*.2.1		X						

Visit Type		Clinic Visit	Clinic Visit	**PhoneCall**	Clinic Visit	**Phone Call**	Clinic **Visit**	**Phone** Call	**PhoneCall**
Study **period**		**Screening**	**Treatment**	**Tre.itment**	**Treatment**	**Treatment**	**Treatment**	**Fdlowup**	**Followup**
Study Day			**1**	3, 5	**4/6**	**15**	29	**91**	**181**
Visit Window **(Days)**		-5 to **1**	0	2 days (-1/+l), 4 days(0/+2) **after vacc**	3/5 da)'S (-1/+l) **after** vacc	**14** days (-2/+2) **after vacc**	**28days** (-7/+14) **after vacc**	90days (-14/+14) **aftel' vacc**	**180** days **(-14/+14) after vacc**
Visit **Number**		**Pre-vacc.ination**	**1**	**NIA**	2	3	**4**	5	***6***
Study Event	References								
SubjectDiary Dispensed with Training	Section 5.2.1		**X**						
SubjectDiary Reminder Call	Section 5.2.2			*xi*	*xi*				
Subject Diary Reviewed and Collected	Section 5.3.1						X		
Assess Unsolicited AEs	Section 7.1		**X**		**X**	**X**	X		
Assess SAEs	Section 7.1.4		**X**		**X**	**X**	X	X	X
Assess for medically attended AEs and AEs leading to withdrawal	Sections 7.I.4.I and7.1.3		**X**		**X**	**X**	X	X	X
Assess relevant medications/ vaccinations	Sections5.1.2 and 6.5	X	**X**		**X**	**X**	X	X	X

Visit Type	Clinic Visit	Clinic Visit	**PhoneCall**	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Phone Call
Study period	Screening	**Treatment**	**Tre.itment**	**Treatment**	**Treatment**	**Treatment**	Follow - up	Follow - up
Study Day		1	3, 5	4/6	15	29	91	**181**
Visit Window (Days)	-5 to 1	0	2 days (-1/+1), 4 da ys (0/+2) after vacc	3/5 da)'S (-1/+1) after vacc	14 days (-2/+2) after vacc	28days (-7/+14) after vacc	90days (-14/+14) **aftel' vacc**	180 days (-14/+14) after vacc
Visit Number	Pre-**vacc.ination**	1	NIA	2	3	**4**	5	***6***
Study Event | References								
Imm unogenicity								
Serology blooddraw | Section 3.5		X"		X		X		
Study C-0mp lerion **Pt·ocedure**								
StudyTennination' | Section *5.5*								X

Notes :

- Subject will berandomized into a blood draw schedule in a I:I ratio. Thesecond clinic visit will occur at Day 4 OR Day *6*.

b Confirm consent fonn(s) signed prior to any procedures.

' Procedure to be performed prior to vaccination

d If the clinicvisit at Day 4 is overlapping with thespecified window of the Day 3 reminder call.the Day 3 reminder call may be omitted.
If the clinic visit at Day *6* is overlapping with the specified window of the Day *5* reminder call, the Day *5* reminder call may beomitted.

- Subjects who tenninate the study early are recommended to complete certain study-related procedures See section *5.5* for further details.

LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Imm1mziation Practices
AE	Adverse Event
CI	Confidence Inteival
CBER	Center for Biologics Evaluation and Research
CRM	Cross Reactive material
CRO	Contract Research Organization
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GMR	Geometric Mean Ratio Geometric
GMT	Mean Titer GlaxoSmithKline
GSK	Vaccines Human Serum
hSBA	Bactericidal Assay Investigator's
IB	Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IM	Intramuscular
IRB	Institutional Review Board
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
pp	Per Protocol
Ref.	Reference
SAE	Serious Adverse Event
SOC	System Organ Class
SOP	Standard Operating Procedure

l. BACKGROUl"-D M 'D RATIONALE

1.1 Background

Neisseria meningitidis is a leading cause of bacterial meningitis and sepsis worldwide, capable of causing outbreaks and epidemics of invasive disease. Meningococcal disease is associated with high morbidity and mortality even among patients who receive early antibiotic treatment. Most cases of invasive disease worldwide are caused by serogroups A, B, C, W and Y.

The quadrivalent meningococcal oligosaccharide diphtheria CRM-197 conjugate vaccine (MenACWY-CRM; Menveo, GSK Vaccines) is approved for active immunization of individuals from 2 months through 55 years of age in the United States. As of February 2015, more than 30,000 of subjects have been exposed to MenACWY-CRM vaccine in completed clinical studies and more than 24 million doses of the vaccine have been distributed globally.

The US Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination with a quadrivalent conjugated meningococcal vaccine for adolescents at **11-**12 years of age with a booster dose administered 5 years later. While a substantial body of data exists showing a robust immune response and good antibody persistence after a single dose of MenACWY-CRM in adolescents, the response to a booster dose of MenACWY-CRM in this age group has only been evaluated in 2 clinical studies with limited number of subjects.

A robust anamnestic immune response to a booster dose of Menveo vaccine administered at approximately 5 years after previous vaccination with the same vaccine or a licensed meningococcal polysaccharide vaccine (Menomune®) was demonstrated in the phase 2 clinical study V59P6El . High titers of bactericidal antibodies against the vaccine serogroups were achieved at 7 and 30 days after booster dose in MenACWY-CRM-primed subjects. However, the number of subjects included in this study was relatively small (N=101, including 50 subjects who received a booster dose after the primary MenACWY-CRM vaccination).

In the phase 3b clinical study V59Pl3 El , a booster dose of MenACWY-CRM was given 3 years after primary vaccination with either MenACWY-CRM or Menactra®(a meningococcal diphtheria toxoid-conjugated MenACWY vaccine, MenACWY-D) in adolescents. A booster dose was able to substantially increase antibody titers against all 4 serogroups irrespective of the priming vaccine. Again, only small number of subjects (N=160) received the MenACWY-CRM booster, (83 who received primary MenACWY-CRM and 77 who received MenACWY-D).

In the light of the current ACIP recommendation for a booster dose of MenACWY-CRM, there exists a need to evaluate the response to a MenACWY-CRM booster given at - 5 years after primary vaccination in meningococcal-vaccine primed adolescents. Generation of this data would also be of relevance in outbreak management and vaccination of travelers to endemic areas.

1.2 Rationale

The purpose/aim of this study is to assess the safety and antibody response to vaccination with a booster dose of Menveo given 4-6 years after primary vaccination and the response to a single dose given to vaccine-naive subjects, and to describe the immune response over time after a single dose of Menveo, dminisli>red to su b j ects previous ly vaccinated with Menveo or Menactra or to vaccine-naive subjects. The inclusion of vaccine-naive subjects in a separate study arm is to enable comparison of the rapidity and magnitude of an anamnestic response to a booster dose (in primed individuals) or the primary response to a first dose (in naive individuals) of MenACWY-CRM.

2. OBJECTIVES

2.1 Plimary Objective(s)

Plimary Immunogeoicity Objective(s)

1. To demonstrate a sufficient immune response following a single dose of MenACWY-CRM (Menveo) vaccine, given to subjects who previously received Menveo or Menactra, as measured by the percentage of subjects with hSBA seroresponse against *N. m.eningitidis* serogroups A, C, W and Y at Day 29 after vaccination

   Criteria to demonstrate immune response sufficiency: The immune response will be considered as sufficient if the lower limit of the one-sided 97.5% CI for percentage of subjects with hSBA seroresponse against serogroups A, C, W and Y is greater than 80% (in pooled group of subjects who received primary vaccination with Menveo or Menactra).

2.2 Seco nd a r y O bjec ti ve(s)

Seco nd a r y I m m un oge nicity O bjec ti ve(s)

1. To compare the immunogenicityof a single dose of MenACWY-CRM vaccine, between subjects who previously received Menveo, subjects who previously received Menactra and vaccine-naive individuals, as measured by the percentage of subjects withhSBA titer ;,:8, with hSBA seroresponse, and hSBA GMTs against *N. meningitidis* serogroups A, C, W and Y at Day 29 after vaccinat ion
2. To compare the immune responses over time following a single dose of MenACWY-CRM vaccine, between subjects who previously received Menveo, subjects who previously received Menactra and vaccine-naive individuals, as measured by the percentage of subjects with hSBA titer 8 and hSBA GMTs against *N. meningitidis* serogroups A, C, Wand Y at Day 1, Day 4, Day 6, and Day 29 after vaccination .
3. To assess persistence of bactericidal antibodies against serogroups A, C, Wand Y at approximately 4-6 years after the primary vaccinat ion with Menveo and after the primary vaccination with Menactra in comparison with naturally-acquired level in vaccine-naive individuals, as measured by the percentage of subjects with hSBA titer 8 and hSBA GMTs at Day 1.
4.

Secondary Safety Objective(s)

1. To assess reactogenicity and safety of MenACWY-CRM vaccine when administered to subjects who previously received Menveo or Menactra and vaccine-naive individuals.

2.3 Exploratory Objective(s)

There are no exploratory objectives.

3. STUDY DESIGN

3.1 Overview of Study Design

This is a phase 3b, controlled, open-labe multi-center study to evaluate safety and immunogenicity of MenACWY-CRM after a single vaccination in healthy individuals who were vaccinated with Menveo or Menactra 4 to 6 years ago and in vaccine-naive individuals

Study population: Approximately 700 healthy subjects 15 through 55 years of age will be enrolled in the study.

Duration of the study: The duration of this study is approximately 6 months per subject.

Written informed consent and, as applicable according to local guidelines, written assent will be obtained before conducting any study-specific procedures.

Vaccination schedule: All subjects will receive a single dose of MenACWY-CRM at Day 1.

Study groups:

Group Menveo-Menveo: approximately 300 subjects, who were vaccinated with a single dose of Menveo 4 to 6 years ago, will receive one dose of MenACWY-CRM.

Group Menactra-Menveo approximately 300 subjects, who were vaccinated with a single dose of Menactra 4 to 6 years ago, will receive one dose of MenACWY-CRM.

Group Naive: approximately 100 subjects equally enrolled across all clinical sites, who have not received any meningococcal vaccination, will receive one dose of MenACWY-CRM.

Randomization / Stratification:

Within each study group, subjects will be randomized into one of two different blood draw schedules according to a 1:1 ratio, described as follows:

- Subjects getting blood draws at Day 1, Day 4 and Day 29.
- Subjects getting blood draws at Day 1, Day 6 and Day 29.

For a schematic overview, see Table 1

Table 3.1-1: Schematic diagram of the VS9_77 study gro ups

Vacd ne History	Vaccination in cwTent study	Blood draw schedule
Menveo N=300	Menveo	Blood draw Day I, 4, 29 (N=150)
		Blood draw Day I, 6, 29 (N= l 50)
Menactra N=300	Menveo	Blood draw Day I, 4, 29 (N=150)
		Blood draw Day I, 6, 29 (N= l 50)
Vaccine-Naive N=IOO	Menveo	Blood draw Day 1, 4, 29 (N=50)
		Blood draw Day 1, 6, 29 (N=50)

Blinding: open-label study.

Blood sanmles: Three (3) blood samples of approximately 10 mL each will be collected according to the blood draw schedule in Table 3.1.1.

Data collection: Electronic Case Reporting Form (eCRF).

Study clinic visits: Three (3) clinic visits at Day I, Day 4 or Day 6 and Day 29 are planned for eachsubject.

Reminder Phone calls: Two (2) reminder phone calls willbe conducted at Day 3 and Day S after the study vaccination to remind the subject/ legal guardian to complete the diary card.

Safety phone calls: Three (3) safety phone calls (at Day IS, Day 91 and Day 181) will be conducted to collect any medically-attendedAEs, AEs leading to withdrawal, SAEs, related medications and any vaccinations. In addition, all unsolicited AEs and related medications occurring after the vaccination will be collected during the safety call at Day IS. The Day 181 Safety Phonecall will also serve as the termination visit.

Solicited Adverse Events (injection site pain, erythema, induration, fatigue, headache, myalgia, arthralgia, loss of appetite, nausea, chills and fever) occurring on the day of vaccination and the following six days (Day 1 through Day 7) willbe recorded daily using a Diary Card for all subjects.

Unsolicited AEs occurring within 28 days after studyvaccination will be collected. Qualified site staffwillinterview the subject by phone approximately 14 days after vaccination and in person at the studysite approximately 28 days after studyvaccination to assess the occurrence of any unsolicited AEs.

Medically-attended AEs, AEs leading to study withdrawal and SAEs will be collected during the entire study period. These data will be captured by interviewing the subject and/or subjects' parents / guardian (as applicable) during the site visits and phone calls and by review of available medical records. Subjects and/or parents / guardian will be encouraged to call the site in the event of any medically-attended AEs or any AEs which they perceive as being of concern during the entire study period.

Table 3.1-2: Schematic diagram of the V59_77 study design

Day 1	Day 4	Day 6	Day 15	Day 29	Day 91	Day 181
Blood draw (all subjects) Menveo	Blood draw (50¾ of subjects)	Blood draw (50% of subjects)	Safety Phone call	Blood draw (all subjects)	Safety Phone call	Safety Phone call Study termination

3.2 Study Period

Each subject should expect to participate in the study for 6 months, from the time of enrolment through the last study visit.

3.3 Blinding Prncedures

The trial is designed as an open-label study.

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/Vaccination.s
- Information on the blood samples.

All data collected must only be identified using the Subject ID, as described in section S.1.4, Randomization.

3.4.2 Tools Used for Data Collection

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

Subject Diary

Paper Diaries (pDiaries), hereafter referred to as Subject Diaries will be the only source document allowed for solicited local and systemic adverse events (including body temperature measurements), starting after the initial, 30 minute post-vaccination period at the clinic. The following additional rules apply to documentation of safety information collected in the Subject Diary.

The Investigator or delegated staff should monitor the Subject's Diary status throughout the study for compliance and any solicited local and systemic adverse events that were of concern to the subject.

- No corrections or additions to the information recorded by the subject or parent(s)/legal guardian(s) within the Subject Diary will be allowed after it is delivered to the site.
- Any blank or illegible fields on the Subject Diary must be described as missing in the eCRF.

Case Report Forms

This study utilizes electronic Case Report Forms (eCRFs) to collect study-related data from each subject. A qualified site staff member(s) is required to enter subject data in the eCRFs in English based on the medical information available in each subject's source record.

Data should be entered into the eCRF in a timely fashion following each subject's clinic visit, study procedure, or phone call. Each subject's eCRF 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.

The following additional rules apply to documentation of Subject Diary information collected in the eCRFs:

- The site must enter all readable entries in the Subject Diary into the eCRF, including those values that may be biologically implausible (e.g. body temperature: 400°C).
- Any illegible or implausible data should be reviewed with the subject and/or parent(s)/legal guardian(s). 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 eCRF (e.g., if the subject above confinns 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 eCRF).

- Any newly described safety infonnation (including a solicited adverse event) nrust not be written into the Subject Diary andnrust 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 EventeCRF.

3.5 Collection of Clinical Specimens

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

- Blood.
- Urine for pregnancy testing (As per routine practice, specimens willbetested at each site).

Processing of a specimen should be completed bya qualified site member and in accordance with the study-specificClinical Specimen Laboratory Manual. Testing of serum specimens willbe performed by a GSK or a designated laboratory. Refer to the study-specific Clinical Specimen Laboratory Manual for additional details.

Blood Specimens

Approximately 10 mL sample of blood willbedrawn from all subjects at visit Day 1 before vaccination, and at visit Day 4 or Day 6 and Day 29. The blood volume willnot exceed 10mL at each time point in order to provide the necessary serum volume (approximately half of the blood draw volume) for the serology assays.

The blood will be used for immunological assays. See section 7, Assessments for additional details.

The total amount of blood collected over the study period per subject will be approximately 30mL.

U1in e S p eci m e ns

Urine willbecollected for pregnancy testing in females of child bearing potential. Urine willbecollected at visit Day 1 before vaccination and the results recorded in the source document and eCRF.

3.6 Stopping/Pausing Guidelines

There are no predetermined stopping rules in this study. Subjects may be withdrawn from the study according to investigator discretion as described in section 3.8, Premature Withdrawal from Study.

3.7 Data Monit01ing Co mmittee

No DMC will be utilized for the study.

3.8 Premature \Vithdrawal 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 safetyreasons. 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 nrust 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 before or 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 S.5.1, Early Termination Visit 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.

AdverseEvent

For anysubject 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 nrust be identified on the AE eCRF page by indicating "Withdrawn from study due to AE". Any ongoing AEs at the time of studywithdrawal 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 Tennination eCRF page and the associated SAE that led to the death must be reported.

\ Vith drawal of consent

The subject and/or parent(s)/legal guardian(s) 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 and/or parent(s)/legal guardian(s) intends to withdraw consent from the study, the investigators 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.

If a subject and/or parent(s)/legal guardian(s) withdraws consent but does not revoke the HIPAA authorization, the Sponsor will have full access to the subject's medical records, including tennination visit information. If a subject and/or parent(s)/legal guardian(s) revokes only the **HIP AA** authorization, the Sponsor will have full access to all of the subject's medical records prior to the date and time of written revocation.

Lo st to Follow-Up

For subjects who fail to show up for final visits (clinic or telephone contacts), or for three consecutive visits, study staff are 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 and/or parent(s)/legal guardian(s) to encourage the completion of study termination procedures. These efforts to contact the subject should be recorded in the source document. The termination date for the subject to be captured on the Study Tennination eCRF page is the date of the last successful 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 discontinuation for insurance issues, moving, no time, etc. This reason should be noted in the Study Tennination eCRF page and any ongoing AEs at the time of study withdrawal should be followed until resolution/stabilization, if possible.

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 eCRF 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, despite the protocol requirement for adequate contraception should be encouraged to continue participating in the study for safety follow-up only. The site must complete a Pregnancy Report CRF (initial report) as soon as possible after learning of pregnancy occurrence (see section 7.1.6, Pregnancies 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 follow-up 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.

Evaluation of the primary and/or secondary immunogenicity/efficacy objectives requires the testing of biological samples from the 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 the last clinic visit, Day 29. 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 Day 29 visit.

If the completion of testing occurs prior the completion of the Last Subject Last Visit (LSLV) the latter date defines the end of study visit.

4. SELECTION OF STUDY POPULATION

4.1 Inclusion C1iteria

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

1. Individuals of IS through SS years of age on the day of informed consent or assent.
2. Individuals who received Menveo 4 to 6 years prior to enrollment at an age of 11 years or older (Menveo-Menveo group)

   OR

   Individuals who received Menactra 4 to 6 years prior to enrollment at an age of 11 years or older (Menactra-Menveo group)

   OR

   Individuals who have not received any previous meningococcal vaccine (Naive group).
3. Individuals who have voluntarily given written informed consent *or* assent after the nature of the study has been explained according to local regulatory requirements, prior to study entry. If the subject is under age 18 at the tinie of enrollment, the parent(s) l1egal *guardian(s)* of the subject should have voluntarily given written informed consent.
4. Individuals who can comply with study procedures including follow-up.[2]

S. Males

Or

Females of non-ciiildbearing potential[3]

Or

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[2] A subject and/or parent(s)/Jegal guardian(s) is/are considered to be compliant if the Investigator judges that the subject will complete the Subject Diary and return for all the follow-up visits scheduled in the study.

[3] A female is considered to be of non-childbearing potential prior to menarche and after natural or induced menopause. Natural menopause is recognized to have occuned after 12 consecutive months of amenorrhea for which there is no other obvious pathological or physiological cause. Induced menopause is recognized to have occurred after hysterectomy, after bilateral oophorecotmy, or iatrogenic ablation of ovarian ftmction.

Females of childbearing potential who are using an effective birth control method[4] which they intend to use for at least 30 days after the last study vaccination.

4.2 Exclusion Criteria

Each subject must not have:

1. History of any meningococcal vaccine administration other than the single vaccination given at 4 to 6 years ago (Menveo-Menveo and Menactra-Menveo groups)

   OR

   History of any meningococcal vaccine administration (Naive group)

2. Current or previous, confirmed or suspected disease caused by *N. meningitidis*.
3. Household contact with and/or intimate exposure to an individual with any laboratory confirmed *N. meningitidis* infection within 60 days prior to study vaccination.
4. Progressive, unstable or uncontrolled clinical conditions.
5. Hypersensitivity, including allergy, to any component of vaccines, medicinal products or medical equipment whose use is foreseen in this study.
6. Clinical conditions representing a contraindication to intramiscular vaccination (IM) and blood draws.
7. 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 study vaccination.
   c. Administration of antineoplastic and immunomodulating agents or radiotherapy within 90 days prior to study vaccination.

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[4] The following birth control methods are considered effective:
Abstinence
Hormonal contraceptive (such as oral, injection, transdennal patch, implant) if used for at least 30 days prior to informed consent
Diaphragm preferably with spermicide, tubal occlusion device
Intrauterine device (IUD)
Tubal ligation
Male partner using condom preferably with spermicide
Male partner having been vasectomized at least six months prior to informed consent

8. Received immunoglobulins or any blood products within 180 days prior to informed consent.
9. Received systemic antibiotic treatment within 3 days prior to study vaccination or blood draw.
10. Received an investigational or non-registered medicinal product within 30 days prior to study vaccination .
11. Study personnel as an immediate family or household member.
12. Individuals who have received any other vaccines within 7 days (for inactivated vaccines) or 14 days (for live vaccines) prior to vaccination in this study or who are planning to receive any vaccine within 28 days from the study vaccination.
13. Individuals who have experienced a moderate or severe acute infection and/or fever defined as a temperature 38°C (100.4°F) within 3 days prior to study vaccination.
14. Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the subject due to participation in the study.

4.3 C1ite1ia for De.lay of Vaccina tion and/or Blood Sam pling

There may be instances when individuals meet all eligibility criteria for vaccination yet have a transient clinical circumstance which may warrant delay of vaccination: body temperature elevation [38.0° C 100 .4° F) within 3 days prior to intended study vaccination], systemic antibiotic treatment within 3 days prior to study 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.

There is a clinical circumstance that warrants delay of blood collection for immunogenicity assessments in this study. This situation is listed below. In the event that a subject meets this criterion for delay of blood collection, blood collection may proceed once the window for delay has passed.

Subject has received a dose of systemic antibiotics less than 3 days before the intended blood collection.

5. 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 Table4.

Table 5-1 Study Procedures

Visit Category	Procedures
Pre-vaccinationClinic Visit(s)	Section 5.1 describes ptocedures to befollowed prior to study vaccination: informed consent/assent, screening, enrolment, andrandomization
VaccinatiooClinic Visit(s)	Section 5.2 describes ptocedures to befollowed during each clinic visit involvingvaccination: vaccination,post-vaccinationptocedures, and post-vaccination reminders
Post-vaccination Visit(s)	Section 5.3 describes follow-upclinic visits and safety follow-up calls
Unscheduled Visit(s)	Section 5.4 describes possible procedures to be followed at unscheduled clinic visit
Study Termination Visit	Section 5.5 describes ptocedures to befollowed at the last study visit for a subject (may include early termination visit)

5.1 Pre-vaccination Clinic Visit(s)

This section describes the procedures that must be performed for each potential subject prior to vaccination, including obtaining informed consent/assent, screening, enrolment and randomization.

5.1.1 Informed Consent/Assent

"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 willof 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.

"Assent" is a term used to express willingness to participate in research by persons who are by definition too young to give informed consent but who are old enough to understand the proposed research in general, its expected risks and possible benefits, and

theactivities expected of them as subjects. Assent by itself is not sufficient, however. If assent is given, informed consent must still be obtained fromthe subject's parent(s) or legal guardian(s). Local laws define who constitutes a "child," and such definitions dictate whether or not a person can legally consent to participate in a protocol (Levine 1988).

Infonned consent of the parent(s)/legal guardian(s) and assent of subject following local !RB/EC guidance **must** be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent and assent should be documented in the subject source document in addition to maintaining a copy of the signed and dated informed consent. Additional specifics regarding the informed consent and assent processes are located in section 13.2, Infonned Consent Procedures.

If a subject and/or parent(s)/legalguardian(s) is unable to read, an impartial witness should be present during the entire informed consent and assent discussion. An impartial witness is defined as a person who is independent from study conduct, who cannot be unfairly influenced by those involved with the study, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject and/or parent(s)/legal guardian(s) and after the subject and/or parent(s)/legal guardian(s) has verbally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject and/or parent(s)/legal guardian(s) and that informed consent was freely given by the subject and/or parent(s)/legal guardian(s).

5.1.2 Screening

After an individual has consented to participate in the study and infonned consent/assent is signed, that individual will be given a unique Screening Number manually created by the investigator. 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 criterialisted in section 4, Selection of Study Population and evaluated during this screening procedure.

Prior to study enrolment, demographic data will be collected from the subject, including: date of birth, gender, race, ethnicity, prior vaccination against meningitis.

Medical history will also be collected, including but not limited to any medical history that may be relevant to subject eligibility for study participation such as prior vaccinations, concomitant medications, and previous and ongoing illnesses or injuries. 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.

Review of systems is a structured interview that queries the subject and/or parent(s)/legal guardian(s) as to any complaints the subject has experienced across each organ system This will be performed before enrolment and used to guide physical examination.

If applicable, prior and concomitant medications or vaccinations taken prior to start of study should be collected (refer to section 6.5, Prior and Concomitant Medications and Vaccines for further details).

Collect vital signs (heart rate, blood pressure, and temperature (preferably taken orally). Measure height and weight.

Perform pregnancy testing in women of childbearing potential (refer to section 3.5, Collection of Clinical Specimens for additional information)

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.

The data collected through study assessments listed above will be written in the source document (see section 9.1, Source Documentation). Should the physical assessment reveal any abnormal values or events, these must be documented in the CRF Adverse Events Form

Prior to vaccination, approximately 10 mL of blood will be drawn from all subjects for the immunological testing see section 3.5, Collection of Clinical Specimens.

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 will be enrolled into the study.

5.1.3 Em·olment

After signing the informed consent/assent fonn, if an individual is determined to be eligible for study participation, the investigator will emoll the subject.

5.1.4 Randomization

Upon entering subject demographic data in IRT, the systemwill assign a 7 digit subject ID number consisting of the 3 digit site number and 4 digit order of randomization at the site. Access to IRT can be obtained by the site staffeither via web or telephone (as back up). The Subject ID will be the subject' s unique identification number for all CRFs and associated study documentation that will be used for duration of the study. After randomization, the Screening Number ceases to be used and remains in the Screening and Enrolment Log only.: During the randomization transaction in IRT Subjects will be assigned a kit number for Menveo vaccination and will be randomized to a blood draw schedule (1:1 according to previous vaccination status).The list of randomization assignments is produced by the IRT service provider and approved by GSK Randomization Office according to applicable GSK Standard Operating Procedure (SOP).

IRT will also be used to ensure adequate and appropriate distribution of enrolment of naivesubjects across all sites. Further details may be found in study-specific plans, for eg, the IRT User Manual and the Randomization Configuration Document.

If for any reason, after signing the infonned consent form (ICF), the subject who is eligible and enrolled fails to be randomized, this is called a randomization failure and the early termination studyprocedures nrust 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 (SDA). 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, Screening.

If for any reason, after randomization the subject fails to undergo treatment, this is an Early Termination and the reason should be recorded in source document as specified in the SDA. The information on these Early Termination subjects should be kept distinct in the source documentation from randomization failures.

Within each study group, subjects will be randomized into one of two different blood draw schedules according to a 1:1 ratio, described as follows:

- Subjects getting blood draws at Day 1, Day 4 and Day 29.
- Subjects getting blood draws at Day 1, Day 6 and Day 29.

If for any reason, after enrolment the subject fails to undergo treatment/study procedures this is an Early Termination and the reason should be recorded in source document as specified in the Source Data Agreement (SDA). The information on these Early Termination subjects should be kept distinct in the source documentation from subjects who are screen failures, as described in section 5.1.2, Screening.

5.2 Vaccination Clinic Visit

The first vaccination will be performed on Day 1.

For studies which have visits for concomitant vaccinations or treatments, see section 6.5, Prior and Concomitant Medications and Vaccines for those visit procedures.

Ensure all blood samples are taken p1ior to the vaccination.

After completing the pre-vaccination procedures on day 1, administer the vaccine to the subject according to the procedures described in section 6.3, Vaccine Preparation and Administration. Observe the blinding procedures described in section 3.3, Blinding Procedures.

Prior to administrationof study vaccination, confirm that the subject does not meet any criteria for delaying additional study vaccinations as described in section 4, Selection of Study Population.

5.2.1 Post-vaccination Procedures

The following post-vaccination procedures will be performed on day 1.

- After vaccination, the subject will be observed for at least 30 minutes including observation for unsolicited adverse events, solicited adverse events, and body temperature measurement. Record all safetydata collected during this time in the subject's source document.
- A Subject Diary will be used in this studyto document solicited adverse events. The Subject Diary is the only source for collection of these data; therefore, it is critical that the subject completes the Subject Diary correctly. The subject should be trained on how and when to complete eaclJ field of the Subject Diary.
- The subject and/or parent(s)/legal guardian(s) should be trained on how to self-measure localsolicited adverse events. The measurement of solicited local adverse events is to be performed using the ruler provided by the site.
- The subject and/or parent(s)/legal guardian(s) should be instructed how to perform bodytemperature measurement using the thermometer provided by the site. If the subject feels unusually hot or cold during the day, the subject and/or parent(s)/legal guardian(s) should check body temperature. If the subject has fever, the highest body temperature observed that dayshould 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 and/or parent(s)/legal guardian(s), but if a person other than the subject and/or parent(s)/legal guardian(s) enters infonnation into the Subject Diary, this person's identity must be documented in the Subject Diary or subject' s source record. Any individual that makes entries into the Subject Diary must receive training on completion of the Subject Diary at the time of the visit. Tilis training must be documented in the subject's source record.

The same individual should complete the Subject Diary throughout the course of the study.

- The site should schedule the next study activity clinic visit on Day 4 or Day 6 depending to which blood draw schedule subject was randomized to with the subject and/or parent(s)/legalguardian(s).

The subject and/or parent(s)/legal guardian(s) will be reminded to complete the Subject Diary and to contact the site if there are any questions, and to contact the siteimmediately (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 or to a visit to/by a doctor or is of concern.

5.2.2 Post-vaccination Reminders

Reminder calls or alerts are not intended to be an interview for collection of safety data. If the subject and/or parent(s)/legal guardian(s) wishes to describe safety infonnation, this information should only be collected by a healthcare professional at the site, and the safety data described must be written down in the subject's medical chart.

Subject Diary Reminder Calls

Subject Diary reminder calls will be performed on day 3 and day S. The purpose of this callis to remind the subject and/or parent(s)/legal guardian(s) about completion of the Subject Diary. The call follows the Subject Diary Reminder Telephone Call Script provided to the site. The subject and/or parent(s)/legalguardian(s) should be reminded to contact the site via the telephone number provided in the informed consent to discuss medical questions. If the clinic visit at Day 4 or Day 6 overlaps with the specified window of the Day 3 or Day S reminder call, the Day 3/Day S reminder call maybe omitted.

5.3 Post-vaccination Visit(s)

Post-vaccinationvisits will be performed on Day 4 or Day 6according to the blood draw schedule to which subject was randomized and Day 29.

5.3.1 Follow-up Clinic Visit.(s)

Fo llow -up clinic visits willbeperformed on Day 4 or Day 6 according to the blood draw schedule to which subject was randomized and on Day 29.During the follow-up clinic visit:

- Subject Diary will be reviewed at Day 29. No changes to the infonnation recorded within the Subject Diary are permissible. For details on the Subject Diary see sections 3.4.2, Tools Used for Data Collection and 5.2.1, Post-vaccination Procedures. The subject and/or parent(s)/legal guardian(s) willbeinterviewed 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. This interview willfollowa script which willfacilitate the collection of relevant safety information. The healthcare professional reviewing these data willdiscuss the symptoms (if any) reported by the subject and willdetermine if any additional diagnoses and/or adverse events are present. Adverse events reported by the subject and/or parent(s)/legal guardian(s) at this follow-up clinic visit must be recorded in the subject's source documentand on an Adverse Events CRF, as specified in section 7.1, Safety Assessment, and not written on the script used for the interview.
- Performa brief symptom-directed physical examination if necessary according to symptoms the subject has reported. This is a physical examination that willinclude an examination of organ systems that are relevant to the investigator based on review of the subject's reported adverse events, concomitant medication use. This assessment may include: measurement of vital signs, body temperature and a check of general appearance. The physical assessment must be performed by the investigator or designee of the investigator, who is qualified to perform a physical assessment in accordance with their institutional policy. Corresponding information is documented in the subject' s source document and CRF(s).
- Collect a blood sample (see section 3.5, Collection of Clinical Specimens for additional information).

The site should schedule the next study activity safety call withthe subject and/or parent(s)/legal guardian(s).

The subject and/or parent(s)/legal guardian(s)] willreceive a written reminder of the next planned study activity. The subject and/or parent(s)/legal guardian(s) will bereminded to contact the site if there are any questions and to contact the siteimmediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalizationor an emergency roomvisit.

5.3.2 Safety Follow-upCalls

Safety follow-up call will be performed on Day 1S, Day 91 and Day 181.

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 and/or parent(s)/legalguardian(s) will be inteIViewed according to the script, and information related to unsolicited adverse events (only at Day 1S), serious adverse events (SAEs), medically attended adverse events, AEs leading to withdrawal and concomitant medications or vaccinations associated with those events will be reviewed. 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.

Thesite should schedule the next study activity with the subject and/or parent(s)/legal guardian(s).

The subject and/or parent(s)/legal guardian(s) 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 hospitalizationor an emergency room visit.

5.4 Unscheduled Visits

Unscheduled visits are not expected within this protocol.

5.5 Study TerminationVisit

The study termination visit willoccur on Day 181. The termination visit will be a telephone call. The date of termination is the date of the last contact (clinic visit or telephonecall)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 S.S.1, Early Termination Visit.

During the telephone call, the following procedures will be performed: inteIView of subject and/or parent(s)/legal guardian(s) to collect medically attended adverse events, AEs leading to withdrawal, SAEs, as well as inteIView of subject and/or parent(s)/legal guardian(s) to collect concomitant medications/ vaccinations associated with those events. All safety information described by the subject nrust be written down in a designated

location within the source document and not written on the script used for the telephone call.

The site will review with the subject and/or parent(s)/legal guardian(s) the plan of when infonnation relating to the subject's participation in the study may be available (e.g., study results, treatment assignments). It will also be discussed how infonnation relating to the subject's participation in the study will be shared with the subject's healthcare provider, if the subject and/or parent(s)/legalguardian(s) chooses to share this infonnation.

The site willcomplete the tennination 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 notifythe Sponsor and, when possible, will perform the procedures listed below. The reason(s) for the early tennination will be included in the subject's source documentation. If the EarlyTermination Visit is a telephone call, collect as much infonnation 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 willbe performed: interview of subject and/or parent(s)/legal guardian(s) to collect adverse events, medically attended adverse events, AEs leading to withdrawal, SAEs, interview of subject and/or parent(s)/legalguardian(s) to collect concomitant medications/ vaccinations.

The site will review with the subject and/or parent(s)/legal guardian(s) the plan of when infonnation 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 and/or parent(s)/legalguardian(s) chooses to share this infonnation.

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

6. 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 below. The study vaccines specific to this study is the **MenACWY-CRM** vaccine (Menveo®, GSK).

The Meningococcal ACWY conjugate vaccine is obtained by extemporaneous mixing just before injection of the lyophilized MenA-CRM component with the MenCWY-CRM fullliquid vaccine. The pharmaceutical form is Powder and solution for solution for injection. Menveo® is provided as vial/vial presentation. MenA lyophilised conjugate component (glass vial) and MenCWY liquid conjugate component (glass vial). After reconstitution, MenACWY-CRM will have the following composition per O.S mL of injectable solution (SeeTable 6.1-1):

Table 6.1-1: MenACWY-CRM Composition

Name of Ingredient	Unit and/or Percentage Formula (Dose 0.5 mL)
Drug Substances	
CRM191-MenA conjugate	10 µg MenA, 16.7- 33.3 µg CRM191
CRM191-MenC conjugate	5 µg MenC, 7.1 - 12.5 µg CRM197
CRM191-MenW conjugate	5 µg MenW, 3.3- 8.3 µg CRM191
CRM191-MenY conjugate	5 µg MenY, 5.6- 10 µg CRM197
Sodium chloride	4.5mg
Excipients	
Sucrose	12.5 mg
Sodium phosphate buffer Sodium dihydrogen phosphate Disodium hydrogen phosphate dehydrate	!OmM 2.5mM 7.5mM
Potassium dihydrogen phosphate	5mM
Water for Injection	q.s 0.5 mL
Volume of Formulation	0.6mL

Name of Ingredient	Unit and/ol' Percentage Fol'mula (Dose 0.5 mL)
Appearance	Colotless tolight yellow
Vaccine Presentation	Asingle dose of two vials

One 0.5 mL dose ofMenACWY will be administered by intranruscular (IM) injection in the deltoid area of non-dominant arm (preferably.)

For more detailed information, refer to the latest version of Investigator Brochure and SPC for Menveo®, which are included in the investigator site file.

6.2 Non-Study Vaccines

Not applicable.

6.3 Vaccine Pr epa rntion and Administra tion

The investigator or designee will beresponsible for oversightof 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 personnel who are qualified to perform that function under applicable local laws and regulations for the specific study site.

All studyvaccines to be administered to the subjects must be stored in a safe and locked place with no access by unauthorized personnel.

The study vaccines will be stored at the defined temperature range (i.e. +2 to +8 C). The storage temperature of the vaccines will bemonitored daily with temperature monitoring devices and willberecorded.

Any temperature deviation, i.e. temperature outside the range (+2 to +8°C), must be reported to the sponsor as soon as detected. Following the exposure to such a temperature deviation, vaccines will not be used until written approval has been given by the sponsor.

The study vaccine should be allowed to reach room temperature before administration, according to local vaccination practice.

MenACWY-CRM (Menveo) vaccine is prepared by aseptically withdrawing all fluid fromthe vial containing the MenCWY-CRM liquid conjugate component and injecting the liquid into the vial containing the MenA-CRM lyophilized portion. Invert and shake the vial well until the vaccine is dissolved. The finalmixed vaccine is then ready for administrationof the MenACWY formulation (0.5 mLJdose of injectable solution).

Detailed vaccine preparation and administration instructions will be provided to investigators in the Protocol Ancillary Document prior to study start.

PRECAUTIONS TO BE OBSERVED IN ADMINISTERINGSTUDY 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 dministration is detennined by evaluating the entry criteria outlined in protocol sections 4.1, Inclusion Criteria and 4.2, Exclusion Criteria.

Eligibility for non-study vaccines should be determined by the investigator, pending the review of the package insert of the relevant vaccine.

Study vaccines should not be dministered 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 should 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 Adminish·ation En or 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 dministration error or overdose is associated with a serious adverse event, it must be reported as such within 24 hours to the Sponsor.

6.5 Plior and Concomitant Medications and Vaccines

All medications, vaccines and blood products taken or received by the subject within 30 days prior to the start of the study are to berecorded on the Prior and Concomitant Medications CRF.

In addition, the following are considered prior medications for this protocol: all medication/vaccines described in theinclusion and exclusion criteria of this protocol including:

- Systemic administration of corticosteroids (PO/IV/IM) for more than 14 consecutive days within 90 days prior to study vaccination;
- Administration of antineoplastic anrl iroro1momodulating agents or radiotherapy within 90 days prior to study vaccination;
- Tmmnnnglobulins or anyblood products within 180 days prior to informed consent;
- Systemic antibiotic treatment within 3 days prior to study vaccination or blood draw;
- Any investigationalor non-registered medicinal product within 30 days prior to study vaccination;
- Administration of vaccines within 7 days (for inactivated vaccines) or 14 days (for live vaccines) prior to vaccination in this study or who are planning to receive any vaccine within 28 days from the study vaccination

Use of analgesics/antipyreticsto prevent or treat solicitedAEs will be captured in the Subject Diary from day 1-7 following each vaccination. Medications taken for prophylaxis arethose intended to prevent the onset of symptoms. Medications taken for treatment are intended to reduce or eliminate the presence of symptoms that are present.

Concomitant medications include all prescription and non-prescription medications (including vaccines) taken by/administered to the subject during the 30 days after study vaccination and must be documented on the Concomitant Medications CRF. Mineral supplements and vitamins are not considered concomitant medications.

When recording concomitant medications/vaccine,sthey should be checked against the study entry and continuation criteria in section 4, Selection of Study Population to ensure that the subject should be enrolled/continue in the study.

Concomitant medication dministered for treatment of AEs with medically-attended visits, AEs leading to study withdrawal andSAEs must be documented during the entire study period.

Any vaccine not foreseen in the studyprotocol in the period starting at Day1 and ending at Day 181 must be recorded in the eCRF.

6.6 Vaccine Supply, Labeling, Storage and Tracking

The Sponsor willensure the following

- Supply the study vaccine(s).
- Appropriate labeling of allstudyvaccines 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 ofthestudy vaccines bya designatedstaffmember atthesite, 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 designatedstorage location

  Confirmation by the Sponsor that the vaccines are authorized for use.

- Proper storage of the studyvaccines, 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:

  Not use of vaccines prior to receipt of authorization for use fromthe 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 administrationof vaccines tostudy 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 bemaintained in an accountability log that will be reviewed by the site monitor.

- Reconciliation of all vaccines received from the Sponsor. Reconciliation is defined as mairitaioiog 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/practicestocks 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 studyvaccines, packaging and supplementary labels are destroyed locally (upon approval fromSponsor) or returned to the Sponsor or to the Depot for destruction.

7. ASSESSMENTS

7.1 Safety Assessment

The measures of safety used in this study are routine clinical procedures. They include a close vigilance for, and stringent reporting of, selected local and systemic adverse events routinely monitored in vaccine clinical 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 abnonnal 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 of 180 days 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 source document. However, any AEs occurring prior to receipt of any study vaccine will be analyzed separately from " treatment emergent" AEs (AEs occurring after dministration 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 and/or parent(s)/legal guardian(s) for 7 consecutive days, using a pre-defmed Subject Diary.

The following solicited adverse events are included in the Subject Diary. Each adverse event is to be assessed using the scoring system reported in parentheses below:

Solicited Local Adverse Events

Injection site pain, erythema, induration, Solicited Systemic Adverse Events

Fatigue, headache, myalgia, arthralgia, loss of appetite, nausea, chills and fever.

Table 7.1.1-1 Severity grading for solicited local and systemic AEs

	]',fild	**Moderate**	**Se.vel'e**
Pain	No inteiference with dailyactivity	Inteiferes with daily activity	Prevents daily activity
Erythema	25-50mm	51- IOOmm	>1 OOmm
lnduration	25-50 mm	51- IOOmm	>1 OOmm
Fatigue	No inteiference with dailyactivity	Inteifereswith daily activity	Prevents daily activity
Headache	No inteiference with activity	Inteifereswith daily activity	Prevents daily activities
Myalgia	No inteiference with activity	Inteifereswith daily activity	Prevents daily activities
Arthralgja	No inteiference with activity	Interfereswith daily activity	Prevents daily activities
Loss ofappetite	Eating less than usual with no effect on normal activity	Eating less thanusual / inteifered with normal activity	Not eating at all
Nausea	No inteiference with dailyactivity	Inteiferes with daily activity	Prevents daily activity
Chills	No inteiference with activity	Inteiferes with daily activity	prevents daily activities

Fever is defined and measured by a body temperature 38.0°C(100.4F). Route of temperature measurement is preferably oral.

Other Indicators of Reactogenicity:

- Use of analgesics / antipyretics for prophylaxis (Days 1-7)
- Use of analgesics / antipyretics for treatment (Days 1-7)
- Body temperature, described in degrees Celsius and summarized by route of measurement and in *05°C* increments from 36.·oc.

The study staff must review the data entered into the Subject Diary as described in section 3.4.2, Tools Used for Data Collection and section S.3.1, Follow-up Clinic Visit(s).

Note: Anysolicited adverse event that meets any of the following criteria must be entered into subjects' source document (see section 9.1, Source Documentation) and also as an adverse event on the Adverse Event CRF:

- Solicited local or systemic adverse event that continues beyond day7 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, Evaluation of Adverse Events).
- Solicited local or systemic adverse event leading to thesubject withdrawing fromthe study or the subject being withdrawn from the study by the investigator (adverse event leading to withdrawal, see section 7.1.3, Evaluation of Adverse Events).
- Solicited local or systemic adverse event that otherwise meets the definition of a serious adverse event (see section 7.1.4, Serious Adverse Events).

7.1.2 UnsolicitedAdverse Events

An unsolicited adverse event is an adverse event that was not solicited using a Subject Diary and that was spontaneously communicated bya subject and/or parent(s)/legal guardian(s) who has signed the informed consent.

Potential unsolicited AEs may be medically attended (defined as symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a health care provider), or were of concern to the subject and/or parent(s)/legal guardian(s). In case of such events, subjects and/or parent(s)/legal guardian(s) will be instructed to contact the site as soon as possible to report the event(s). The detailed information about the reported unsolicited AEs willbe collected by the qualified site personnel during the interview and will be documented in the subject's records.

Unsolicited AEs that arenot medically attended nor perceived as a concern by subjects and/or parent(s)/legal guardian(s) will be collected during interview with the subject [and/or parent(s)/legalguardian(s) and by review of available medical records at the next visit (see section 5.3, Post-vaccination Visit(s).

7.1.3 Evaluation of Adverse Events

Everyeffort 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 "otitismedia").

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, Solicited Adverse Events.

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.
- AEs leading to withdrawal: adverse events leading to study or vaccine withdrawal.

If solicited or unsolicited adverse events have been reported and the subject and/or parent(s)/legal guardian(s)] indicated that the symptoms required medical attendance or were of concern, the subject and/or parent(s)/legal guardian(s) must be contacted for further information.

When the subject and/or parent(s)/legal guardian(s) is contacted for any of these reasons, the contact must be documented in the subject's source documentation.

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 The investigator's assessment of ongoing Adverse Events at the time of each subject's last visit should be documented in the subject's medical chart.

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 occUITed); 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 definiiton, 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, Evaluation of Adverse Events).

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 cUITent 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 occUITed 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

Adverse Events of Special Interest (AESIs) will not be assessed during the study.

7.1.S Methods for Recording Adverse Events and Serious Adverse Events

Findings regarding Adverse Events must be reported on an Adverse Events CRF, as specified in section 7.1.1, Solicited Adverse Events, 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 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 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/ IRB 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/IRB and other relevant authorities.

7.1.S.1 Post-Study Events

Any SAE that occurs outside of the protocol-specified follow-up period and 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 1 month after Last Subject Last Visit (LSLV). 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 or delegate 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 GSK or delegate. 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, Serious Adverse Events) must also be reported on the VSAE Report Form.

7.1.7 Safety Laboratory Measurements

No safety laboratory measurements will be done in this study.

7.2 Efficacy Assessment

This section is not applicable. This study has no efficacy measurements.

7.3 Immunogenicity Assessment

The functional measure of immunogenicity used in this study, Serum Bactericidal Assay (SBA), is a measure of the ability of antibodies, in concert with human complement, to kill meningococci, and is widely used and generally recognized as the serological correlate of protection The key measures of immunogenicity will be the percentages of subjects with seroresponse[1], percentages of subjects who achieve hSBA titers 8 and, and the hSBA GMTs against serogroups A, C, W and Y reference strains

These measurements will be assessed in serology samples collected at Visit Day 1, 4 or 8 and Day 29. The measures of immunogenicity used in this study are standard, i.e., widely

[1] Seroresponse to N. meningitidis serogroups A, C, W and Y is defined as: for subjects with a pre-vaccination hSBA titer < 4, a post-vaccination hSBA titer 2:8; for subjects with a pre-vaccination hSBA titer 24, an increase in hSBA titer of at least four times the pre-vaccination titer.

used and generally recognized as reliable, accurate, and relevant (able to describe the quality and extent of the immune response).

All subjects will have a blood draw at Day I, before vaccination. Subsequent blood draws willbe at either Day 4 or Day 6 post vaccination, and at Day 29 post vaccination.

Primary:

Collected samples may be used in other assays, for test improvement or development of analytical methods related to the study vaccines or the disease under evaluation to allow a more reliable measurement of the vaccine response. Under these circumstances, additional testing on the samples may be performed by GSK outside the scope of the protocol Any sample testing willbe done in line with the consent of the individual subject's parent/ guardian.

Testing willbe conducted by qualified and certified laboratories. All assays will be performed in GSK, Clinical Laboratory Sciences, or a delegate laboratory.

8. STATISTICAL CONSIDERATIONS

8.1 Endpoints

8.1.1 Plimai-y En dpoint(s)

8.1.1.1 P1im ary Safety Endpoint(s)

There are no primary safety endpoints in this study.

8.1.1.2 P1imar y Efficacy Endpoint(s)

There are no primary efficacy endpoints in this study.

8.1.1.3 P1imary Immunogenicity Endpoint(s)

Thefollowing measure willbe summarized for the pooled (Menveo-Menveo and Menactra-Menveo) group

1. Percentage of subjects with hSBA seroresponse[5] against *N. meningitidis* serogroups A, C, W and Y at Day 29.

8.1.2 Secondary Endpoint(s)

8.1.2.1 Secondary Safety Endpoint(s)

Safety of the study vaccine willbe assessed in the pooled vaccine group (Menveo-Menveo and Menactra-Menveo) and the vaccine-naivegroup in teimsof the frequency (percentage) of reported adverse events including

1. Any unsolicited AEs reported within 30 minutes after vaccination;
2. Solicited local and systemic AEs reported from Day 1 (6 hours) through Day 7 after vaccination;
3. Other indicators of reactogenicity (e.g. use of analgesics/ antipyretics, body temperature) within 7 days after vaccination;
4. All unsolicited AEs reported from Day 1 through Day 29 after vaccination;

[5] Seroresponse is defined as: a) post-vaccination hSBA?:8 for subjectswith a pre-vaccination hSBA <4; b) for subjects with a pre-vaccinationhSBA ?:4, an increase of at least four timesthe pre-vaccinationhSBA.

5. Medically-attended AEs, AEs leading to withdrawal and SAEs reported from Day 1 through Day 181 (entire study period).

Adverse events will be coded using MedDRA preferred terms as applicable.

8.1.2.2 Secondary Efficacy Endpoint(s)

There are no secondary efficacy endpoints in this study.

8.1.2.3 Secondary Immunogenicity Endpoint(s)

The following measures will be nmmari:i:ed for Menveo-Menveo, Menactra-Menveo, Naive and the pooled (Menveo-Menveo and Menactra-Menveo) groups unless otherwise noted:

1. Percentage of subjects with hSBA titer 8 against *N. meningitidis* serogroups A, C, W and Y at Day 1, Day 4, Day 6 and Day 29;
2. Percentages of subjects with hSBA seroresponse against *N. meningitidis* serogroups A, C, W and Y at Day 4, Day 6 and Day 29 (Day 29: Except the pooled group);
3. hSBA GMfs against N. *meningitidis* serogroup A, C, W and Y at Day 1, Day 4, Day 6 and Day 29;
4. Ratios of hSBA GMfs at Day 1, Day 4, Day 6 and Day 29 (between study groups).
5. Ratios of hSBA GMfs at Day 4, Day 6, and Day 29 compared to Day 1 (within study groups).

8.1.3 Exploratory Endpoint(s)

8.1.3.1 Exploratory Safety Endpoint(s)

There are no exploratory safety endpoints in this study.

8.1.3.2 Exploratory Efficacy Endpoint(s)

There are no exploratory efficacy endpoints in this study.

8.1.3.3 Exploratory Immunogenicity Endpoint(s)

There are no exploratory immunogenicity endpoints in this study.

8.2 Success Criteria

8.2.1 Success Criteria for Primary Objective(s)

8.2.1.1 Success Criteria for Primary Safety Objective(s)

There are no primary safety objectives in this study.

8.2.1.2 Success Criteria for Primary Efficacy Objective(s)

There are no primary efficacy objectives in this study.

8.2.1.3 Success Criteria for Primary Immunogenicity Objective(s)

To demonstrate immune response sufficiency after MenACWY-CRM booster vaccine administration, the lower limit of the one-sided 97.5% Confidence Interval(CI) for percentage of subjects with hSBA seroresponse against each of serogroups A, C, W and Y must be greater than 80% (in the pooled group of subjects who received primary vaccination with Menveo or Menactra). The threshold of80% was previously agreed for demonstration of immune response adequacy in other age groups (e.g. in infants, study VS9_36).

8.2.1.3.1 Rationale for Combining the Menveo-Menveo and Menach·a-Menveo groups

Table 8.2.1.3.1-1 shows excerpt of data from a previous study (VS9P13El) assessing the immunogenicity of a booster dose of Menveo among subjects who had previously been vaccinated with either Menveo or Menactra 3 years prior in another study (VS9P13) while subjects were 11-18 years old. The table shows almost identical seroreponse rates and 95% Cls at one-month post-booster dose of Menveo for subjects previous vaccinated with Menveo and Menactra. This suggests that data from the two groups can be pooled or combined for analysis of seroresponse following a booster dose of Menveo as planned in the current study VS9_77.

Table 8.2.1.3.1-1: hSBA Seroresponse at One Month Following the Booster at 3 Years After Vaccination, by Serogroup - Booster- PP Population

Vaccination	ACWY/ACWY Group IV	MenactJ"a/ A Y GroupV	Difference' G1·onpIV - G1·onpV
Overall Seroresponse	68 (97%) (90-100) N=70	70(100%) (95-100) N=70	(-3%) (-10-2)
Overall Seroresponse	66 (93%) (84-98) N=71	65 (93%) (84-98) N=70	(0%) (-9-10)
Overall Seroresponse	63 (91%) (82-97) N=69	64 (93%) (84-98) N=69	(-! %) (-11-8)
Overall Seroresponse	63 (90%) (80-96) N=70	65 (93%) (84-98) N=70	(-3%) (-13-7)

Source: Table 14.2.1.7 of Clinical Study Report for V59P13El; 'Data represented as (difference in %)(95% CI of difference).

8.2.2 Success Cli teria for Secondar y Objective(s)

8221 SuccessC1i telia for Secondary Safety Objective(s)

There are no success criteria associated with the secondary safety objectives.

8222 Success Cli telia for Secondary Efficacy Objective(s)

There are no secondary efficacy objectives in this study.

8223 Success Clitelia for Secondary Immunogenicity Objective(s)

There are no success criteria associated with the secondary immunogenicity objectives in this study.

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

Solicited Safety Set (solicited local and systemic adverse events and other solicited adverse events)

All subjects in the Exposed Set with any solicited adverse event data.

Unsolicited Safety Set (unsolicited adverse events)

All subjects in the Exposed Set with unsolicited adverse event data.

Overall Safety Set

All subjects who are in the Solicited Safety Set and/or Unsolicited Safety Set.

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

Full Analysis Set Immunogenicity

FAS <Day 1)

All subjects in the All Enrolled Set who:

- are randomized;

- provide evaluable serum samples at Day 1 whose result is available for at least one serogroup.

FAS (Day4)

All subjects in the All Enrolled Set who:

- are randomized;
- receive the study vaccination;
- provide evaluable serum samples at Day 1 whose result is available for at least one serogroup (except for hSBA titer 8, GMTs and between-group GMRs calculated at specific timepoints); and
- provide evaluable serum samples at Day 4 whose result is available for at least one serogroup.

FAS (Day6)

All subjects in the All Enrolled Set who:

- are randomized;
- receive the study vaccination;
- provide evaluable serum samples at Day 1 whose result is available for at least one serogroup (except for hSBA titer 8, GMTs and between-group GMRs calculated at specific timepoints);
- provide evaluable serum samples at Day 6 whose result is available for at least one serogroup.

FAS (Day29)

All subjects in the All Enrolled Set who:

- are randomized;
- receive the study vaccination;
- provide evaluable serum samples at Day 1 whose result is available for at least one serogroup (except for hSBA titer 8, GMTs and between-group GMRs calculated at specific timepoints);
- provide evaluable serum samples at Day 29 whose result is available for at least one serogroup.

In case of vaccination error, subjects in the 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.S Per Protocol (PP) Set Efficacy/Immunogenicity Set

A PPS will be defined for each FAS described in the previous Section with additional criteria specified below.

All subjects in the FAS Immunogenicity who

- Correctly receive the study vaccine (i.e., receive the vaccine to which the subjects is randomized and at the scheduled time points).
- Have no protocol deviations leading to exclusion (see section 8.3.8, Protocol Deviations) as defined prior to unblinding / analysis.
- Are not excluded due to other reasons defmed prior to unblinding or analysis (see section 8.3.8, Protocol Deviations)

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

Subjects who withdrew informed consent.

8.3.6 Other Analysis Sets

There are no other analysis sets used in this study.

8.3.7 Subgroups

Using the FAS (Day 29), the analyses of the primary objectives will be replicated by center; gender; and race.

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. CSR-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

8.4.1 Analysis of Demographic and Baseline Characteristics

Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age, height and weight at enrolment will be calculated overall and by study group.

Distributions of subjects by sex and ethnic origin will be summarized overall and by study group.

8.4.2 Analysis of Primary Objective(s)

8.4.2.1 Analysis of Primary Safety Objective(s)

There are no primary safety objectives in this study.

8.4.2.2 Analysis of Primary Efficacy Objective(s)

There are no primary efficacy objectives in this study.

8.4.2.3 Analysis of Primary Immunogenicity Objective(s)

8.4.2.3.1 Statistical Hypotheses

Null hypothesis: $P_i \leq 0.80$

versus

Alternative hypothesis: $P_i > 0.80$

Where: P_i is the population seroresponse rate for the pooled Menveo-Menveo and Menactra-Menveo group; $i = 1, 2, 3, 4$ refer to serogroup A, C, W and Y respectively. The level of significance is fixed at one-sided 0.025.

8.4.2.3.2 Analysis Sets

The analysis population to be used for the primary objectives is the FAS (Day 29) Set. Analyses of primary objectives will be repeated on the PPS (Day 29) to assess robustness of results.

8.4.2.3.3 Statistical Methods

General

Missing immunogenicity values are assumed MCAR (Missing Completely At Random) and therefore may not contain information that impact the result of the analysis (i.e., not informative). Imputation methods will therefore not be used.

Overall significance level for all hypothesis tests is one-sided $\alpha = 2.5\%$.

Seroresponse (Day 29)

Seroresponse is defined as: a) post-vaccination hSBA titer 8 for subjects with a pre-vaccination hSBA titer <4; b) for subjects with a pre-vaccination hSBA titer 4, an increase of at least four times the pre-vaccination hSBA.

For each ACWY serogroup, the percentage of subjects with seroresponse will be computed, along with associated two-sided 95% Clopper-Pearson Cls.

Further details of the statistical methods will be provided in the SAP.

8.4.3 Analysis of Secondary Objective(s)

8.4.3.1 Analysis of Secondary Safety Objective(s)

8.4.3.1.1 Analysis of Extent of Exposure

Subjects will be analyzed to the extent that they were exposed to study vaccines and according to the available safety data for the subject during any study period. Subjects who withdraw early or who are lost to follow-up will be removed from the summary table denominator for the time period in which they have no available safety data collected.

8.4.3.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events

All solicited adverse events will be summarized according to defined severity grading scales.

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 7 will be summarized for the intervals Day 1 (6 hours) - Day 3, Days 4-7, Day 1 (6 hours) - Day 7 by maximal severity and by study group. Separate analyses will be performed for solicited AEs reported 30 minutes after vaccination. The severity of solicited local adverse events, including injection-site erythema and induration, will be categorized based on linear measurement: None (0-24 mm), Mild (25-50 mm), Moderate (51-100 mm), Severe (> 100 mm).

Injection site pain and systemic reactions, including fatigue, headache, myalgia, arthralgia, chills, nausea, loss of appetite, occurring up to 7 days after each vaccination 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'.

Use of antipyreticsand analgesics will be summarized by frequency, by type of use (prophylactic versus treatment) and percentage of subjects reporting use.

Body teJl1)erature will be summarized separately according to the 3 schemes described below and will be broken down according to route of measurement:

- by O.S °C increments from 36.0°Cup to ,::40°C;
- by 1°C increments: <36.0, 36.0-36.9, 37.0-37.9, 38.0-38.9, 39.0-39.9, ,::40°C;
- According to different cut-offs (< versus ::::): 38 .0, 38 .S, 39 .0, 39.S , 40 .0 °C .

8.4 .3 .1. 3 An al ys i s o f U n so li cited Advene 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 dateof first vaccination. AE starting prior to the first vaccination willonly 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 thenbe grouped by MedDRA preferred terms into frequency tables according to system organ class (SOC).

All reported adverse events, as well as adverse events judged by the investigator as at least possibly related to study vaccine, willbe summarized according to SOC and preferred term within SOC. These summaries will be presented by study group 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 willbe counted.

Separate summaries will be producedfor the following categories:

- Adverse events that are possibly or probably related to vaccine
- Unsolicited AEs reported within 30 minutes after vaccination
- Unsolicited AEs reported within 30 days after vaccination
- Adverse events leading to withdrawal
- Adverse events leading to a medically attended visit
- Serious adverse events

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.

8.4.3.1.4 Statistical Hypotheses

There are no statistical hypotheses associated with the secondary safety objectives.

8.4.3.1.S Analysis Sets

Analyses of solicited adverse events - and other solicited reactions - and unsolicited adverse events will be performed on the relevant safety sets.

8.4.3.1.6 Statistical Methods

For unsolicited adverse events, the entirestudy period will be divided into the following intervals: onset within30 minutes after vaccination , onse t within 28 days after vaccination; and from Day 1 through Day 181. For solicited adverse events, the solicited study period will be divided into intervals: from 6 hours through day 3; from day 4 throughday 7; and from 6 hours through day 7.

No imputation methods will be used to address missing safety data.

SnmmariPS of safety will be presented using frequencies and percentages within each study group. No statistical comparisons among the studygroups with respect to any of the safety parameters will be performed.

8.4.3.2 Analysis of Seconda ry Efficacy Objective(s)

There are no secondary efficacy objectives associated with this study.

8.4.3.3 Analysis of Seconda ry Immun ogenicity Objective(s)

8.4.3.3.1 Sta tistical Hypotheses

Analyses related to the secondary immunogenicity objectives will be descriptive; no formal statistical tests will be performed.

8.4.3.3.2 Analysis Sets

Analysesof secondary imm1mogenicity will be based on the FAS and repeated on the PPS.

8.4.3.3.3 StatisticalMethods

General

The hSBA titers at each visit will be logarithmicallytransformed (baselO) to obtain approximately nonnally distributed data.

For comparison of percentages and GMT ratios, unadjusted estimates will be obtained along with adjusted estimates from regression models to account for potential baseline imbalance between study groups.

For each*N. meningitidis* serogroup A, C, Wand Y, unadjustedGMTs will be calculated, withtheir associated two-sided 95% Cls, by exponentiating the corresponding log-transformed means and their 95% Cls. Adjusted GMR.s will be obtained from Analysis of Covariance (ANCOVA) models.

See section 8.4.2.3.3 for other relevant details.

Seroresponse (Day 29)

The percentage of subjects with seroresponse and associated two-sided 95% Clopper-Pearson Cls will be computed by group (Menveo-Menveo, Menactra-Menveo, and Naive) and*N. meningitidis* serogroups **A,** C, W and Y test strains. Differences in percentages and associated 95% Cls between study groups will be calculated using the Miettinen & Nurminen score method.

In a descriptive fushion - using the difference in percentages and 95% Cls - each of the previously vaccinated groups will be compared to the nai:Ve group . Also the two previously vaccinated study groups will be compared to each other.

As sensitivity analyses, the difference in percentages will also be obtained from a log-linear model adjusting for center and pre-vaccinationtiter. Please see SAP for technical details.

Percentage of Su bjects \Vith hSBA titere::8 (Da y I , Da y 4, Da y 6, and D ay 29)

For each study group and in the pooled group, the percentage of subjects with hSBA titer 8 andassociatedtwo-sided 95% Clopper-Pearson Cls will be computed by the *N. meningitidis* serogroups A, C, W and Y test strains on Day 1, Day 4, Day 6 and Day 29 (as applicable, depending on blood draw schedule).

Differences in percentages and associated 95% Cls between study groups will be calculated using the Miettinen & Nurminen score method.

In a descriptive fashion - using the difference in percentages and 95% Cls - the previously vaccinated groups (individually and pooled) will be compared to the naive group. Also the two previously vaccinated groups will be compared to each other.

As sensitivity analyses, the difference in percentages will also be obtained from a log-linear model adjusting for center and pre-vaccination titer. Please see SAP for technical details.

Between-gr oup Ratios of Gl\lT s (Ad jus ted an d U na d ju sted)

The between -group ratio ofhSBA GMTs and corresponding 95% CI, at each of Visit Day 1 (Persistence), Day 4, Day 6 and Day 29 against each *N. meningiti.dis* serogroups A, C, W and Y test strains will be obtained by exponentiating the mean between-group differences in log-transformed titers and the corresponding 95% Cls at each of the timepoints specified.

Additionally, adjusted ratio of GMTs will be obtained from ANCOVA models including center and pre-vaccination titer as factors in the model.

The previously vaccinated groups (individually and pooled) will be compared to the naive group at each timepoint - descriptively - using the ratios of GMTs.

The two previously vaccinated groups will be compared at each timepoint using GMT ratios.

\Within-gro up Ratios of Gl\lT s (Ad jus ted an d U na d ju sted)

Within each study group and for each antigen/serotype, ratios of GMT will be calculated, as applicable, at:

- Visit Day 4 versus at Visit Day 1;
- Visit Day 6 versus at Visit Day 1; and
- Visit Day 29 versus at Visit Day 1.

The unadjusted GMRs and 95% Cis will be constructed by exponentiating the mean within-group differences in log-transformed titers and the corresponding 95% Cls.

Adjusted GMRs will be obtained from Analysis of Covariance (ANCOVA) models including center as factor in the model. Further details of the statistical methods will be provided in the Statistical Analysis Plan (SAP).

8.4.4 Analysis of Exploratory Objectives

8.4.4.1 Analysis of Exploratory Safety Objective(s)

There are no exploratory safety objectives in this study.

8.4.4.2 Analysis of Exploratory Efficacy Objective(s)

There are no exploratory efficacy objectives in this study.

8.4.4.3 Analysis of Exploratory Immunogeoicity Objective(s)

There are no exploratory immunogenicityobjectives in this study.

8.5 Sample Size and Power Considerations of Primary Objectives

Statistical power was estimated based on observed data from study V59P13E1, where seroresponse rates at one-month post booster dose ofMenACWY-CRM ranged from 97% (90%-100%) to 100% (95%-100%)for serogroup A, 93% (85%-98%) for serotype C; 91% (82%-97%) to 93% (84%-98%) for serogroup W; and 90% (80%-96%) to 93% (84%-98%) for serogroup Y among subjects printed with MenACWY-CRM or Menactra in the three years preceding the study.

Assuming the trueseroresponse rates in the pooled group range from 90% to 97% (alternative hypothesis) for each serotype, a sample size of n=540will have at least 96% power to show sufficiency of immune response to a booster dose of MenACWY-CRM in the pooled group, compared with a pre-specified reference seroresponse of 80% (null hypothesis) using an exact test with 0.025 one-sided significance level. When taking a 10% dropout rate into account, N=600 previously vaccinated subjects have to be enrolled in the study. Calculations have been done with nQuery Advisor (Version 7.0).

Table 8.5-1: Statistical Power to Test for Sufficiency of Immune Response Given a Range of True Seroresponse Rates for Evaluable Sample Size of 540 subjects

Serotype	True Seroresponse Rate	Power
A	0.97	0.99
C	0.93	0.99
W	0.91	0.99
Y	0.90	0.99
Total Power		0.96

8.6 Interim Analysis

No interim analysis of data from this studyis planned.

9. SOURCE DOCUMENTATION, STUDY MONITORING AND AUDITING

In order to ensure consistency across sites, 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 protoco allapplicable studyprocedures, documentation practices and all electronic systems. CRFs supplied by the Sponsor must be completed for each randomized subject (see section 8.3.1, All Enrolled Set 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/or parent(s)/legal guardian(s) and date of completion and reason.

The subject and/or parent(s)/legal guardian(s) must also allow access to the subject's medical records. Each subject and/or the parent(s)/legal guardian(s) 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 safetydata 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, thesesources 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, GSK or its designee (e.g., a CRO) will develop a Clinical 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 GSK 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 GSK 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. .

Data verification may also be performed through a centralized review of data (e.g., checking for outliers or other anomalies). 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 GSK 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. DATA MANAGEME1''T

10.1 Data Enh·y 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 onto case report fonns (CRFs) in a timely fashion by the investigator and/or the investigator's dedicated site staff. Data entered onto CRFs are stored on a secure website. The data collected on this secure website are assimilated into an electronic data capture (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 nrust review data entered and electronicallysign the CRFs to verifytheir accuracy.

Access to the EDC system for data entryor review will require training and distinct individual access code assignments to those site staffmembers who willbe 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.

10.2 Data Cla1ifi cation

As part of the conduct of the trial, the Sponsor may havequestions 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 willensure the confidentiality of their medical information in accordance with all applicablelaws and regulations.

11. 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 representativebefore disposal of any studyrecords, andmust notify the Sponsor of any change in the location, disposition, or custody of the study files. Essential documents must be retained for 1S 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 immnoogenicity samples, provided that the integrity of the stored sample permits testing.

12. USE OF JIl,'FORMATION AND PUBLICATION

GSK assures that the key design elements of this protocol willbe posted in a publicly accessible database such as clinicaltrials.gov, and in compliance with cUITent 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 theend of study as defined in section 3.9, End of Study.

In accordance with standard editorial, ethical practices and cUITent guidelines of Good Publication Practice (Graf 2009), GSK will generally support publication of multicenter studies only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement prior to the start of the study. The coordinating investigator will also sign the clinical study report on behalf of the principal investigators (CPMP/EWP/2747/00). Authorship willbe determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any fonnal publication of the studyin which contribution ofGSK personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate GSK personnel.

Novartis 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. ETIDCAL CONSIDERATIONS

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 withthe ICH HarmonizedTripartite Guidelines for GoodClinical Practice, with applicable local regulations including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry ofHealth, Labor, and Welfare, 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, Informed Consent/Assent. 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 studydocuments. 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 studybefore anystudy-related procedures are conducted. The informed consent process may be conducted up to *5* days prior to vaccination on Day I. If the subject and/or legal guardian(s) is unable to read and write, a witness must be present during the infonned 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 the GSK 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. If case of doubts on the ability of a subject to adhere to these requirements, that subject should not be allowed in the study

Before the start of the study, the investigator willhave the informed assent, the informed consent, and any other materials that will be provided to the subject and/or parent(s)/legal guardian(s) reviewed and approved by the IRB/EC. This review and approval willbe documented and stored with other study documents. The investigator or designee must fully inform the subject and/or parent(s)/legalguardian(s) of all pertinent aspects of the study. A copy of the written informed consent and informed assent willbegiven to the subject and/or parent(s)/legalguardian(s).

In addition, the investigator or designee should explain pertinent aspects of the study in an age appropriate manner to pediatric subjects who are eligible for informed assent in accordance with local policies. The subject and parent(s)/legalguardian(s) 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 parent(s)/legal guardian(s) must sign the consent/assent forms indicating their agreement to participate in the study before any study-related procedures are conducted. If the subject and/or parent(s)/legal guardian(s) are unable to read and write, a witness must be present during the informed consent/assentdiscussion and at the time of informed consent/assentsignature.

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 (RI), 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 studystart and at any time the protocol is amended during studyconduct, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance withthese 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 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 GSK immediately that thisrequest 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-relatedduties.

- 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 and/or parent(s)/legal guardian(s), 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 nwnber(s)). In addition, the investigato,r or person designated by the investigato,r 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 nrust 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 amendmen,t the investigator is expected to take any inunediate 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. REFERENCE LIST

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Novartis

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The individuals listed have appl'()ved this document for ii!Jplementation using an electronic signature in the Atlas EDMS. tFPO

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