**Clinical Study Protocol**
Sponsor:
**GlaxoSmithKline Biologicals SA**
Rue de l'Institut 89,
1330 Rixensart, Belgium

| | |
|---|---|
| **Primary Study vaccine and number** | • GlaxoSmithKline (GSK) Biologicals' Meningococcal (serogroups A, C, W and Y) oligosaccharide diphtheria $CRM_{197}$ conjugate vaccine, liquid formulation (GSK3536820A) |
| **Other Study vaccine** | • GSK Biologicals' Meningococcal serogroups A, C, W and Y oligosaccharide diphtheria $CRM_{197}$ conjugate vaccine (*Menveo*). |
| **eTrack study number and Abbreviated Title** | 207467 (MENACWY CONJ-069 [V59_78]) |
| **Investigational New Drug (IND) number** | 11278 |
| **EudraCT number** | 2017-003456-23 |
| **Date of protocol** | Final version 1: 25 September 2017 |
| **Date of protocol amendment** | Amendment 1 Final: 17 January 2018<br>Amendment 2 Final: 15 March 2018<br>Amendment 3 Final: 08 February 2019 |
| **Title** | Immunogenicity, reactogenicity and safety study of different formulations of GSK Biologicals' Meningococcal ACWY conjugate vaccine (GSK3536820A and *Menveo*) when administered to healthy adolescents and young adults 10 to 40 years of age. |
| **Detailed Title** | A phase 2b, randomized, controlled, observer-blind, multi-center study to evaluate safety and immunogenicity of different formulations of GSK Biologicals' Meningococcal ACWY conjugate vaccine (GSK3536820A and *Menveo*) administered to healthy adolescents and young adults 10 to 40 years of age. |
| **Co-ordinating author** | • PPD (XPE Pharma & Science for GSK Biologicals) |
| **Contributing authors** | • PPD (Senior Clinical Research and Development Lead)<br>• PPD (Clinical Research and Development Lead) |

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| **Contributing authors (continued)**<br><br>**(Amended 08 February 2019)** | • PPD (Director Clinical Statistics)<br>• PPD ***(Lead Statistician)***<br>• PPD (Study Statistician)<br>• PPD (Study Statistician)<br>• PPD, PPD ***and*** PPD (Study Delivery Lead)<br>• PPD (Clinical Trial Supply Manager)<br>• PPD (Clinical Laboratory Sciences [CLS] Read-out Team Leader)<br>• PPD (Clinical Safety representative)<br>• PPD and PPD (CLS Study Managers)<br>• PPD (Oversight Data Manager)<br>• PPD and PPD (Study Data Managers)<br>• PPD ***(Lead Scientific Writer)***<br>• PPD ***(Scientific Writer)***<br>• PPD (Regulatory Affairs representative)<br>• PPD (Global Patents representative)<br>• PPD (Clinical and Epidemiology Research & Development Project Lead) |

# Protocol Amendment 3 Sponsor Signatory Approval

| | |
|---|---|
| **eTrack study number and Abbreviated Title** | 207467 (MENACWY CONJ-069 [V59_78]) |
| **IND number** | 11278. |
| **EudraCT number** | 2017-003456-23 |
| **Date of protocol amendment** | Amendment 3 Final: 08 February 2019 |
| **Detailed Title** | A phase 2b, randomized, controlled, observer-blind, multi-center study to evaluate safety and immunogenicity of different formulations of GSK Biologicals' Meningococcal ACWY conjugate vaccine (GSK3536820A and *Menveo*) administered to healthy adolescents and young adults 10 to 40 years of age. |
| **Sponsor signatory** | Michele Pellegrini<br><br>Clinical and Epidemiology Research & Development Project Lead |
| **Signature** | |
| **Date** | |

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# Protocol Amendment 3 Rationale

| **Amendment number:** Amendment 3 |
|---|
| **Rationale/background for changes:**<br>• An update in the list of contributing authors has been included on the protocol cover page.<br>• Wording of *Section 5.3 Method of blinding* and *Section 5.7.3 Laboratory assays* has been updated to align with the current Company Standards related to blinding for sample testing. |

# Protocol Amendment 3 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, 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 responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply 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 vaccines and other study-related duties and functions as described in the protocol.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) 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 investigational vaccines, and more generally about his/her financial ties with 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 information it has about such ownership interests and financial ties to regulatory authorities.
- 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** | 207467 (MENACWY CONJ-069 [V59_78]) |
| **IND number** | 11278 |
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| **Investigator name** | _____ |
| **Signature** | _____ |
| **Date** | _____ |



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# Sponsor Information

1. Sponsor

**GlaxoSmithKline Biologicals**
Rue de l'Institut 89, 1330 Rixensart, Belgium

2. **Sponsor Medical Expert for the Study**

Refer to the local study contact information document.

3. **Sponsor Study Monitor**

Refer to the local study contact information document.

4. **Sponsor Study Contact for Reporting of a Serious Adverse Event**

GSK Biologicals Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 8.4.2.

5. **GSK Biologicals' Central Safety Physician On-Call Contact information for Emergency Unblinding**

GSK Biologicals Central Safety Physician and Back-up Phone contact: refer to protocol Section 8.8.

# SYNOPSIS

| | |
|---|---|
| **Detailed Title** | A phase 2b, randomized, controlled, observer-blind, multi-center study to evaluate safety and immunogenicity of different formulations of GSK Biologicals' Meningococcal ACWY conjugate vaccine (GSK3536820A and *Menveo*) administered to healthy adolescents and young adults 10 to 40 years of age. |
| **Indication** | Active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W and Y. |
| **Rationale for the study and study design** | • Rationale for the study<br><br>GlaxoSmithKline (GSK) Biologicals' *Menveo* (Meningococcal serogroups A, C, W and Y oligosaccharide diphtheria $CRM_{197}$ conjugate vaccine; MenACWY) is licensed for use in infants through adults in more than 60 countries. *Menveo* vaccine is delivered as a vial including the liquid MenCWY conjugate components and a vial containing the lyophilized MenA conjugate component. The lyophilized component has to be reconstituted with a liquid component immediately prior to vaccination, which adds to complexity of vaccine administration. Furthermore, vaccine components come in separate vials which make it bulky and consume cold storage space. To simplify the vaccine administration, prevent occurrence of administration errors and to optimize vaccine shipment and storage, a fully liquid formulation of MenACWY vaccine has been developed.<br><br>The aim of this study is to assess the non-inferiority of immune response against the serogroup A between the currently licensed MenACWY vaccine (*Menveo*) and the investigational MenACWY liquid vaccine aged for different lengths of time (approximately 24 months and 30 months) by storage at 2-8℃. The immune responses against serogroups C, W and Y and the reactogenicity and safety profile of the study vaccines will also be evaluated. However, as the CWY component of the investigational vaccine is identical to that of the licensed formulation, non-inferiority will not be assessed for these serogroups. Safety will be evaluated for 6 months after a single dose vaccination.<br><br>The results of this study will provide immunogenicity and safety data to support the determination of the $Menveo_{Liquid}$ shelf-life. Currently, the *Menveo* commercial formulation has a shelf-life of 24 months. For the investigational *Menveo* liquid formulation, the same 24-month shelf-life will be assessed, and a shelf-life of 30 months would be desirable from a commercial standpoint. |

- Rationale for the study design

**Study population:** healthy adolescents and young adults ≥10 to ≤40 years of age (YoA) will be enrolled in this study for the following reasons:

  – The incidence of meningococcal disease is highest in young children <1 year of age (due to immaturity of the immune system). However, there is a second peak in the incidence among adolescents and young adults (due to lifestyle and behavioural risk factors [e.g. physical clustering, exposure to cigarette smoke]).

  – Adolescents are an important target population for meningococcal vaccination as they have the highest rates of meningococcal carriage and transmission. Routine meningococcal vaccination targeting adolescents and young adults is recommended in the US and UK, and some other countries.

  – The dosing schedule in adolescents and adults (single dose) is simpler than in infants (3+1 doses), and there are few other vaccinations routinely recommended in this age range; both factors that augment feasibility of the study.

**Vaccination dose and route of administration:** subjects will receive a single dose of investigational MenACWY liquid vaccine (aged for approximately 24 or 30 months), or licensed MenACWY vaccine (*Menveo*) (i.e. dosing scheme currently indicated for *Menveo* in adolescents and adults).

**Study blinding:** given the different appearance of the investigational liquid and currently licensed MenACWY vaccines, double blinding is not possible and the study will be conducted in an observer-blind manner.

**Objectives**

**Primary**

- To demonstrate non-inferiority of the investigational MenACWY liquid product aged for approximately 24 months to that of currently licensed MenACWY vaccine, as measured by the hSBA GMTs directed against *N. meningitidis* serogroup A at Day 29 after a single dose vaccination.

*Criterion:*

*Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the ratio of hSBA GMTs against serogroup A between the MenACWY liquid vaccine aged for approximately 24 months and the licensed MenACWY vaccine is greater than 0.5.*

- To demonstrate non-inferiority of the investigational MenACWY liquid vaccine aged for approximately 30 months to that of currently licensed MenACWY vaccine, as measured by the hSBA GMTs directed against *N. meningitidis* serogroup A at Day 29 after a single dose vaccination.

  *Criterion:*

  *Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the ratio of hSBA GMTs against serogroup A between the MenACWY liquid vaccine aged for approximately 30 months and the licensed MenACWY vaccine is greater than 0.5.*

Non-inferiority hypotheses testing will be conducted sequentially, starting from vaccine lot aged for approximately 24 months and subsequently with vaccine lot aged for approximately 30 months.

**Secondary**

- To compare the immunogenicity of the investigational MenACWY liquid products aged for approximately 24 or 30 months and the currently licensed MenACWY vaccine, as measured by hSBA GMTs directed against *N. meningitidis* serogroups C, W and Y, at Day 29.
- To compare the immunogenicity of the investigational MenACWY liquid products aged for approximately 24 or 30 months and the currently licensed MenACWY vaccine, as measured by the percentage of subjects with a ≥ 4-fold rise in post vaccination hSBA titer for *N. meningitidis* serogroups A, C, W and Y at Day 29 compared to Day 1.

  Note: A 4-fold rise is defined as: a) for individuals whose pre-vaccination titers are < the limit of detection (LOD), the post-vaccination titers must be ≥ 4-fold the LOD or ≥ the lower limit of quantitation (LLOQ) whichever is greater; b) for individuals whose pre-vaccination titers are ≥ the LOD and ≤ the LLOQ, the post vaccination titers must be at least four times the LLOQ; and c) for individuals whose pre-vaccination titers are > the LLOQ, the post vaccination titers must be at least four times the pre-vaccination titer.

- To compare the immunogenicity of the investigational MenACWY liquid products aged for approximately 24 or 30 months and the currently licensed MenACWY vaccine, as measured by the percentage of subjects with hSBA titer ≥8 and ≥LLOQ* directed against *N. meningitidis* serogroups A, C, W and Y at Day 29.

  * Note: To be assessed for each serogroup if the pre-defined LLOQ value for that serogroup is >8.

- To assess the safety/reactogenicity of the *investigational* MenACWY liquid vaccine aged approximately 24 or 30 months and the currently licensed MenACWY vaccine.

**Study design**

- Experimental design: Phase IIB, observer-blind, randomized, controlled, multi-centric study with two parallel groups per phase, in a two-phase staggered design.
- Duration of the study: The duration of this study is approximately 6 months per subject.
  - Epoch 001: starting at Visit 1 (Day 1) and ending at last Safety contact (Day 181) of phase 2.
- Primary completion Date (PCD): Visit 2 (Day 29).

  Refer to glossary of terms for the definition of PCD.
- End of Study (EoS): Last subject last visit (Phone call 3) or last testing results released of samples collected at Visit 2 (Day 29) of Study Phase 2* if it occurs after LSLV.

  * In this case EoS must be achieved no later than 8 months after LSLV.

  Refer to glossary of terms for the definition of EoS.
- Study groups:
  - **ACWY_Liq24** (Study Phase 1): approximately 417 healthy subjects receiving investigational MenACWY liquid vaccine (GSK3536820A) aged for approximately 24 months at 2-8$^{o}$C;
  - **ACWY_1** (Study Phase 1): approximately 417 healthy subjects receiving currently licensed GSK' MenACWY vaccine (*Menveo*), not aged;

- **ACWY_Liq30** (Study Phase 2): approximately 417 healthy subjects receiving investigational MenACWY liquid vaccine (GSK3536820A) aged for approximately 30 months at 2-8°C;
- **ACWY_2** (Study Phase 2): approximately 417 healthy subjects receiving currently licensed GSK' MenACWY vaccine (Menveo), not aged.

### Synopsis Table 1 Study groups and epochs foreseen in the study

| Study groups | Number of subjects | Age (Min/Max) | Epochs |
|---|---|---|---|
| | | | Epoch 001 |
| ACWY_Liq24* | 417 | 10 years – 40 years | x |
| ACWY_1 | 417 | 10 years – 40 years | x |
| ACWY_Liq30** | 417 | 10 years – 40 years | x |
| ACWY_2 | 417 | 10 years – 40 years | x |

* ACWY_Liq24: vaccine lot aged for approximately 24 months.
** ACWY_Liq30: vaccine lot aged for approximately 30 months.

### Synopsis Table 2 Study groups and treatment foreseen in the study

| Treatment name | Vaccine/product name | Study Groups | | | |
|---|---|---|---|---|---|
| | | ACWY_Liq24 | ACWY_1 | ACWY_Liq30 | ACWY_2 |
| MenACWY liquid | MenACWY liquid | x | | x | |
| Licensed MenACWY (*Menveo**) | MenA lyo | | x | | x |
| | MenCWY liquid | | | | |

* *Menveo* commercial formulation consisting of a MenA lyophilized component and of a MenCWY liquid component to be reconstituted together before administration.

- Control: active control
- Vaccination schedule: All subjects will receive a single dose of study vaccine at Visit 1 (Day 1).
- Treatment allocation: Randomization will be performed at Visit 1 (Day 1) using a central randomization system on internet (SBIR), with stratification to include 40% of subjects from ≥10 to <18 YoA and 60% from ≥18 to ≤40 YoA.
- Blinding: observer-blind for each of the two phases of the study.

### Synopsis Table 3 Blinding of study epochs

| Study Epochs | Blinding |
|---|---|
| Epoch 001 | observer-blind |

- Sampling schedule: Blood sample of approximately 20 ml will be collected from each subject at Visit 1 (Day 1; pre-vaccination) and at Visit 2 (Day 29).
- Type of study: self-contained.
- Data collection: Standardized Electronic Case Report Form (eCRF). Solicited adverse events (AEs) assessed on site during the 30 minutes post-vaccination assessment are to be recorded on the source documents and entered in the eCRF. Solicited AEs occurring after the 30 minutes post-vaccination assessment will be collected using a subject Diary (electronic Diary [eDiary]).

**Number of subjects**

Approximately 1668 subjects (≥10 to ≤40YoA) are planned for enrollment into this study, approximately 417 subjects per group.

**Endpoints**

**Primary**

The following measures will be summarized:

- hSBA GMTs against *N. meningitidis* serogroup A at Day 29, for each vaccine group and between-group ratios (between vaccine groups ACWY_Liq24 and ACWY_1, and ACWY_Liq30 and ACWY_2).

**Secondary**

The following measures will be summarized:

- hSBA GMTs against *N. meningitidis* serogroups A (except Day 29), C, W and Y at Day 1 and at Day 29, for each vaccine group and between-group ratios (between vaccine serogroups ACWY_Liq24 and ACWY_1, and ACWY_Liq30 and ACWY_2).
- Within-group ratios of hSBA GMTs against *N. meningitidis* serogroups A, C, W and Y at Day 29 compared to Day 1, for each vaccine group.
- Percentages of subjects with a ≥ 4-fold rise in post-vaccination hSBA titer for *N. meningitidis* serogroups A, C, W and Y at Day 29 compared to Day 1, for each vaccine group and between-group differences (between vaccine groups ACWY_Liq24 and ACWY_1, and ACWY_Liq30 and ACWY_2).

  Note: A 4-fold rise is defined as: a) for individuals whose pre-vaccination titers are < the LOD, the post-vaccination titers must be ≥ 4-fold the LOD or ≥ the LLOQ whichever is greater; b) for individuals whose pre-vaccination titers are ≥ the LOD and ≤ the LLOQ, the post-vaccination titers

must be at least four times the LLOQ; c) for individuals whose pre-vaccination titers are > the LLOQ, the post-vaccination titers must be at least four times the pre-vaccination titer.

- Percentages of subjects with hSBA titer ≥8 and ≥LLOQ* against *N. meningitidis* serogroups A, C, W and Y at Day 1 and at Day 29, for each vaccine group and between-group differences (between vaccine groups ACWY_Liq24 and ACWY_1, and ACWY_Liq30 and ACWY_2).

  *Note: To be assessed for each serogroup if the pre-defined LLOQ value for that serogroup is >8.

Safety of the study vaccine formulations will be evaluated for all vaccine groups in terms of the frequency (percentage) of reported adverse events including:

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

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| **ADEM** | Acute disseminated encephalomyelitis |
| **AE:** | Adverse Event |
| **ATEAM:** | Advanced Temperature Excursion Analysis and Management |
| **CBER:** | Center for Biologics Evaluation and Research |
| **CDC:** | Centers for Disease Control |
| **CI:** | Confidence Interval |
| **CLS:** | Clinical Laboratory Sciences |
| **CRDL:** | Clinical Research and Development Lead |
| **$CRM_{197}$:** | *Corynebacterium diphtheriae* Cross Reaction Material 197 |
| **eCRF:** | electronic Case Report Form |
| **EoS:** | End of Study |
| **EU:** | European Union |
| **EudraCT:** | European Clinical Trials Database |
| **FAS:** | Full Analysis Set |
| **FDA:** | Food and Drug Administration, United States of America |
| **GBS:** | Guillain-Barré syndrome |
| **GCP:** | Good Clinical Practice |
| **GMR:** | Geometric Mean Ratio |
| **GMT:** | Geometric Mean Titer |
| **GSK:** | GlaxoSmithKline |
| **IB:** | Investigator Brochure |
| **HIV:** | Human Immunodeficiency Virus |
| **hSBA:** | Human Serum Bactericidal Assay |

| | |
|---|---|
| **ICF:** | Informed Consent Form |
| **IAF:** | Informed Assent Form |
| **ICH:** | International Conference on Harmonization |
| **IEC:** | Independent Ethics Committee |
| **IM:** | Intramuscular |
| **IMP:** | Investigational Medicinal Product |
| **ID:** | Identification |
| **IM:** | Intramuscular |
| **IND:** | Investigational New Drug |
| **IV:** | Intravenous |
| **IRB:** | Institutional Review Board |
| **iSRC:** | Internal Safety Review Committee |
| **KD:** | Kawasaki disease |
| **LAR:** | Legally Acceptable Representative |
| **LLOQ:** | Lower limit of quantitation |
| **LSLV:** | Last Subject Last Visit |
| **MACDP:** | Metropolitan Atlanta Congenital Defects Program |
| **MedDRA:** | Medical Dictionary for Regulatory Activities |
| **MenACWY:** | Meningococcal serogroups A, C, W and Y oligosaccharide diphtheria $CRM_{197}$ conjugate vaccines; *Menveo* |
| **MMWR:** | Morbidity and Mortality Weekly Report |
| ***N. meningitidis:*** | *Neisseria meningitidis* |
| **PCD:** | Primary Completion Date |
| **PO:** | Per os, i.e., orally |
| **PPS:** | Per protocol Set |

| | |
|---|---|
| **SAE:** | Serious Adverse Event |
| **SBIR:** | Source DataBase for Internet Randomization |
| **SDL:** | Study Delivery Lead |
| **SDV:** | Source Document Verification |
| **SmPC:** | Summary of Product Characteristics |
| **SPM:** | Study Procedures Manual |
| **TBD:** | To be determined |
| **YoA:** | Years of age |

# GLOSSARY OF TERMS

**Adequate contraception:** Adequate contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label for example:

- abstinence from penile-vaginal intercourse, when this is their preferred and usual lifestyle,
- Combined oestrogen and progesterone oral contraceptives,
- injectable progestogen,
- implants of etenogestrel or levonorgestrel,
- Contraceptive vaginal ring,
- percutaneous contraceptive patches,
- intrauterine device or intrauterine system,
- male partner sterilization prior to the female subject's entry into the study, and this male is the sole partner for that subject,

  The information on the male sterility can come from the site personnel's review of the subject's medical records; or interview with the subject on her medical history.
- male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository), and/or progesterone alone oral contraceptive.

Adequate contraception does not apply to subjects of child bearing potential with same sex partners, or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle.

**Adverse event:** Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

| | |
|---|---|
| **Blinding:** | A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an observer-blind study, the subject and the site and sponsor personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment assignment (see Section 5.3 for details on observer-blinded studies). |
| **Child in care:** | A child who has been placed under the control or protection of an agency, organization, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian. |
| **Eligible:** | Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria. |
| **End of Study**<br><br>**(Synonym of End of Trial)** | For studies without collection of human biologicals samples or imaging data EoS is the Last Subject Last Visit (LSLV).<br><br>For studies with collection of Human Biologicals Samples, EoS is defined either as last subject last visit of the study (LSLV) or as the date of the last testing/reading* released of the Human Biological Samples or imaging data related to primary and secondary endpoints if occurred after LSLV.<br><br>* In this case, EoS must be achieved no later than 8 months after LSLV. |
| **Epoch:** | An epoch is a set of consecutive timepoints or a single timepoint from a single protocol. Epochs are defined to support a main purpose which is either to draw conclusions on subject participation or to draw a complete conclusion to define or precise the targeted label of the product. Supporting means that data collected at the timepoints included in an epoch must be sufficient to fulfil the purpose of the epoch. |

| | |
|---|---|
| | Typical examples of epochs are screening, primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety. |
| **eTrack:** | GSK's tracking tool for clinical trials. |
| **Immunological correlate of protection:** | The defined immune response above which there is a high likelihood of protection in the absence of any host factors that might increase susceptibility to the infectious agent. |
| **Investigational vaccine:**<br><br>**(Synonym of Investigational Medicinal Product)** | A pharmaceutical form of an active ingredient being tested in a clinical trial, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. |
| **Legally acceptable representative:**<br><br>**(The terms legal representative or legally authorized representative are used in some settings)** | An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial. |
| **Menarche:** | Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1-2 years of breast development, thelarche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue). |
| **Menopause:** | Menopause is the age associated with complete cessation of menstrual cycles, menses, and implies the loss of reproductive potential by ovarian failure. A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile at the appropriate age e.g. > 45 years. |
| **Primary completion date:** | The date that the final subject was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated. |

| | |
|---|---|
| **Randomization:** | Process of random attribution of treatment/schedule to subjects in order to reduce bias of selection. |
| **Self-contained study:** | Study with objectives not linked to the data of another study. |
| **Site Monitor:** | An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites. |
| **Solicited adverse event:** | AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period. |
| **Study vaccine/product:** | Any investigational vaccine/product being tested and/or any authorized use of a vaccine/ product /placebo as a reference or administered concomitantly, in a clinical trial that evaluates the use of an investigational vaccine/product. |
| **Subject:** | Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the vaccines or as a control. |
| **Subject number:** | A unique number identifying a subject, assigned to each subject consenting to participate in the study. |
| **Treatment:** | Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject. |
| **Treatment number:** | A unique number identifying a treatment to a subject, according to treatment allocation. |
| **Unsolicited adverse event:** | Any AE reported in addition to those solicited during the clinical study. Also any ‘solicited’ symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event. |

# TRADEMARKS

The following trademarks are used in the present protocol.

Note: In the body of the protocol (including the synopsis), the names of the vaccines will be written in *italics*.

| Trademarks of the GlaxoSmithKline group of companies | Generic description |
|---|---|
| Menveo | Meningococcal (Serogroups A, C, Y, and W-135) oligosaccharide diphtheria $CRM_{197}$ conjugate vaccine |

# 1. INTRODUCTION

## 1.1. Background

*Neisseria (N.) 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.

Based on antigenic differences in their capsular polysaccharide, 13 serogroups of *N. meningitidis* have been identified. Virtually all disease-associated isolates are encapsulated, with serogroups A, B, C, W and Y responsible for the majority of invasive meningococcal infections worldwide [Granoff, 2003; Rosenstein, 2001].

The conjugate vaccines containing capsular oligosaccharides conjugated to a protein carrier have been developed and successfully licensed worldwide. These vaccines induce T cell-dependent immune responses, and are immunogenic also in infants and young children, conferring long lasting protection in all age groups, and priming for immunological memory [Pollard, 2009].

GlaxoSmithKline (GSK) Biologicals' *Menveo* (Meningococcal serogroups A, C, W and Y oligosaccharide diphtheria $CRM_{197}$ conjugate vaccine; MenACWY) is licensed for use in infants through adults in more than 60 countries. In the United States, *Menveo* is approved for active immunization of individuals from 2 months through 55 years of age (YoA). In the European Union (EU), *Menveo* is licensed for the active immunization of children (from 2 years of age), adolescents and adults. As of March 2017, more than 30,000 subjects were exposed to MenACWY vaccine in the GSK sponsored completed clinical studies and more than 28 million doses of the vaccine were distributed globally.

*Menveo* vaccine is delivered as a vial including the liquid MenCWY conjugate components and a vial including the lyophilized MenA conjugate component. The lyophilized component has to be reconstituted with a liquid component immediately prior to vaccination, which adds to complexity of vaccine administration. Furthermore, vaccine components come in separate vials which make it bulky and consume cold storage space. To simplify the vaccine administration, prevent occurrence of administration errors and to optimize vaccine shipment and storage, a fully liquid formulation of MenACWY vaccine has been developed.

The investigational liquid formulation of the MenACWY vaccine contains the same meningococcal serogroups A, C, W and Y oligosaccharides conjugated to $CRM_{197}$ protein as the ones included in currently licensed MenACWY (*Menveo*) vaccine. The amount of oligosaccharides (10 µg for serogroup A and 5 µg for each serogroup C, W and Y) and the injection volume (0.5 mL) are same for both vaccine formulations. The key difference of the investigational MenACWY liquid vaccine is that serogroup A component is not lyophilized and therefore sucrose and potassium dihydrogen phosphate are not included as excipients.

During the manufacturing process the conjugated oligosaccharides are produced by a covalent attachment of the oligosaccharides to the carrier protein. The results of development stability studies indicate that the percentage of free saccharides (FS) for serogroup A will increase over time when stored at temperature of 2-8℃. Oligosaccharides for serogroups C, W and Y, however remain substantially unchanged and no degradation has been observed during stability studies. This is not unexpected, given that the manufacturing and storage processes for the CWY component have not changed from those used for the currently licensed formulation.

Please refer to the current Investigator Brochure for information regarding the pre-clinical and clinical studies and the epidemiological information of the investigational liquid formulation of the MenACWY vaccine.

## 1.2. Rationale for the study and study design

### 1.2.1. Rationale for the study

To compare immunogenicity of the currently licensed MenACWY vaccine with the investigational MenACWY liquid vaccine aged for different lengths of time (approximately 24 months and 30 months) by storage at 2-8℃.

The purpose of the study is to assess the non-inferiority of immune response against the serogroup A between the currently licensed MenACWY vaccine and the investigational MenACWY liquid vaccines aged for two different lengths of time (approximately 24 or 30 months). The immune responses against serogroups C, W and Y and the reactogenicity and safety profile of the study vaccines will also be evaluated. However, as the CWY component of the investigational vaccine is identical to that of the licensed formulation, non-inferiority will not be assessed for these serogroups. Reactogenicity will be evaluated for 7 days, and safety for 6 months after a single dose vaccination.

The results of this study will provide immunogenicity and safety data to support the determination of the $\text{Menveo}_{\text{Liquid}}$ shelf-life. Currently, the *Menveo* commercial formulation has a shelf-life of 24 months. For the investigational *Menveo* liquid formulation, the same 24-month shelf-life will be assessed, and a shelf-life of 30 months would be desirable from a commercial standpoint.

### 1.2.2. Rationale for the study design

**Study population:** healthy adolescents and young adults ≥10 to ≤40 YoA will be enrolled in this study for the following reasons:

- The incidence of meningococcal disease is highest in young children <1 year of age (due to immaturity of the immune system). However, there is a second peak in the incidence among adolescents and young adults (due to lifestyle and behavioural risk factors [e.g. physical clustering, exposure to cigarette smoke]).

- Adolescents are an important target population for meningococcal vaccination as they have the highest rates of meningococcal carriage and transmission. Routine meningococcal vaccination targeting adolescents and young adults is recommended in the US and UK, and some other countries.
- The dosing schedule in adolescents and adults (single dose) is simpler than in infants (3+1 doses), and there are few other vaccinations routinely recommended in this age range; both factors that augment feasibility of the study.

**Vaccination dose and route of administration:** subjects will receive a single dose of investigational MenACWY liquid vaccine (aged for approximately 24 or 30 months), or licensed MenACWY vaccine (*Menveo***)** (i.e. dosing scheme currently indicated for *Menveo* in adolescents and adults).

**Study blinding:** given the different appearance of the investigational liquid and currently licensed MenACWY vaccines, double blinding is not possible and the study will be conducted in an observer-blind manner.

## 1.3. Benefit: Risk Assessment

Please refer to the Prescribing Information for information regarding the summary potential risks and benefits of the licensed *Menveo* vaccine. The risks are anticipated to be the same for the investigational liquid formulation of the MenACWY vaccine.

The following section outlines the risk assessment and mitigation strategy for this study protocol:

### 1.3.1. Risk Assessment

| Important Potential/Identified Risk | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| *Menveo* and investigational MenACWY liquid vaccine | | |
| Important Identified risk: Reconstitution errors | Cases describing medication errors due to administration of the MenCWY conjugate liquid component only without reconstitution with the MenA conjugate lyophilized component, or due to administration of the MenA conjugate lyophilized component only after reconstitution with a different solvent, have been reported during the MenACWY clinical development program. | In several sections of the protocol (e.g., Section 6.1. "Description of study vaccines") it is clarified that the 2 vaccine components have to be reconstituted before vaccine injection. |
| Important potential risk: Guillain-Barré syndrome (GBS) | GBS has been observed with other vaccines. No cases have been reported during the MenACWY clinical development program. | GBS will be monitored through SAE collection. |

| Important Potential/Identified Risk | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| Important potential risk: Acute disseminated encephalomyelitis (ADEM) | ADEM has been observed with other vaccines. Two cases from clinical trials were retrieved from the GSK's global safety database for MenACWY. None of them has provided sufficient evidence of a causal association between ADEM and MenACWY. | ADEM will be monitored through SAE collection. |
| Important potential risk: Thrombocytopenia | Immune thrombocytopenic purpura has been reported in association with several licensed vaccines. Two cases related to MenACWY were reported during the clinical development program, but none of them has provided a clear association between thrombocytopenia and the vaccine. | Immune thrombocytopenic purpura will be monitored through SAE collection. |
| Important potential risk: Facial paresis | Facial paresis was recognized as an important potential risk following the results of a sponsored observational study (V59_34OB) which found an imbalance of cases of facial paresis following vaccination with MenACWY, mainly when administered concomitantly with other vaccines. No cases of facial paresis were reported from interventional clinical trials. | Paralysis of the face is mentioned in the list of side effects in the ICF. Facial paresis will be monitored through SAE collection. |
| Important potential risk: Vasculitis including Kawasaki disease (KD) | There were 7 cases of suspected KD reported in three clinical studies of Menveo. The occurrence of the cases in Menveo studies is consistent with the known epidemiology of KD in terms of geographic and temporal clustering, and seasonal variation. Therefore there is no evidence of a causal association between KD and MenACWY vaccine. As the exposure in clinical trial of subject was limited considering the incidence of the disease, KD is considered as a potential risk. | Vasculitis including Kawasaki disease will be monitored through SAE collection. |

| Important Potential/Identified Risk | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| Study Procedures | | |
| Risk of blood sampling | Blood sampling associated risk of syncope, dizziness, infection at the site after or during venepuncture. | Blood samples will be obtained by a trained professional and medical assistance will be available.<br>The potential risk of feeling faint, or experiencing mild local pain, bruising, irritation or redness at the site where blood was taken, is mentioned in the Informed Consent Form (ICF). The amount of blood to be taken for sampling will not be harmful to the subject's health. |

### 1.3.2. Benefit Assessment

Benefits considerations include:

- Medical evaluations/assessments associated with this study (i.e. physical examination).
- Potential benefit of receiving GSK's investigational or licensed meningococcal vaccine during study duration that may have clinical utility.

### 1.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential or identified risks in association with the investigational and licensed MenACWY vaccine are justified by the potential benefits (prevention) that may be afforded to subject(s) receiving the investigational or licensed MenACWY vaccine.

# 2. OBJECTIVES

## 2.1. Primary objectives

- To demonstrate non-inferiority of the investigational MenACWY liquid product aged for approximately 24 months to that of currently licensed MenACWY vaccine, as measured by the hSBA GMTs directed against *N. meningitidis* serogroup A at Day 29 after a single dose vaccination.

  *Criterion:*

  *Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the ratio of hSBA GMTs against serogroup A between the MenACWY liquid vaccine aged for approximately 24 months and the licensed MenACWY vaccine is greater than 0.5.*

- To demonstrate non-inferiority of the investigational MenACWY liquid vaccine aged for approximately 30 months to that of currently licensed MenACWY vaccine, as measured by the hSBA GMTs directed against *N. meningitidis* serogroup A at Day 29 after a single dose vaccination.

  *Criterion:*

  *Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the ratio of hSBA GMTs against serogroup A between the MenACWY liquid vaccine aged for approximately 30 months and the licensed MenACWY vaccine is greater than 0.5.*

Non-inferiority hypotheses testing will be conducted sequentially, starting from vaccine lot aged for approximately 24 months and subsequently with vaccine lot aged for approximately 30 months.

Refer to Section 10.1 for the definition of the primary endpoint(s).

## 2.2. Secondary objectives

- To compare the immunogenicity of the investigational MenACWY liquid products aged for approximately 24 or 30 months and the currently licensed MenACWY vaccine, as measured by hSBA GMTs directed against *N. meningitidis* serogroups C, W and Y, at Day 29.
- To compare the immunogenicity of the investigational MenACWY liquid products aged for approximately 24 or 30 months and the currently licensed MenACWY vaccine, as measured by the percentage of subjects with a ≥ 4-fold rise in post vaccination hSBA titer for *N. meningitidis* serogroups A, C, W and Y at Day 29 compared to Day 1.

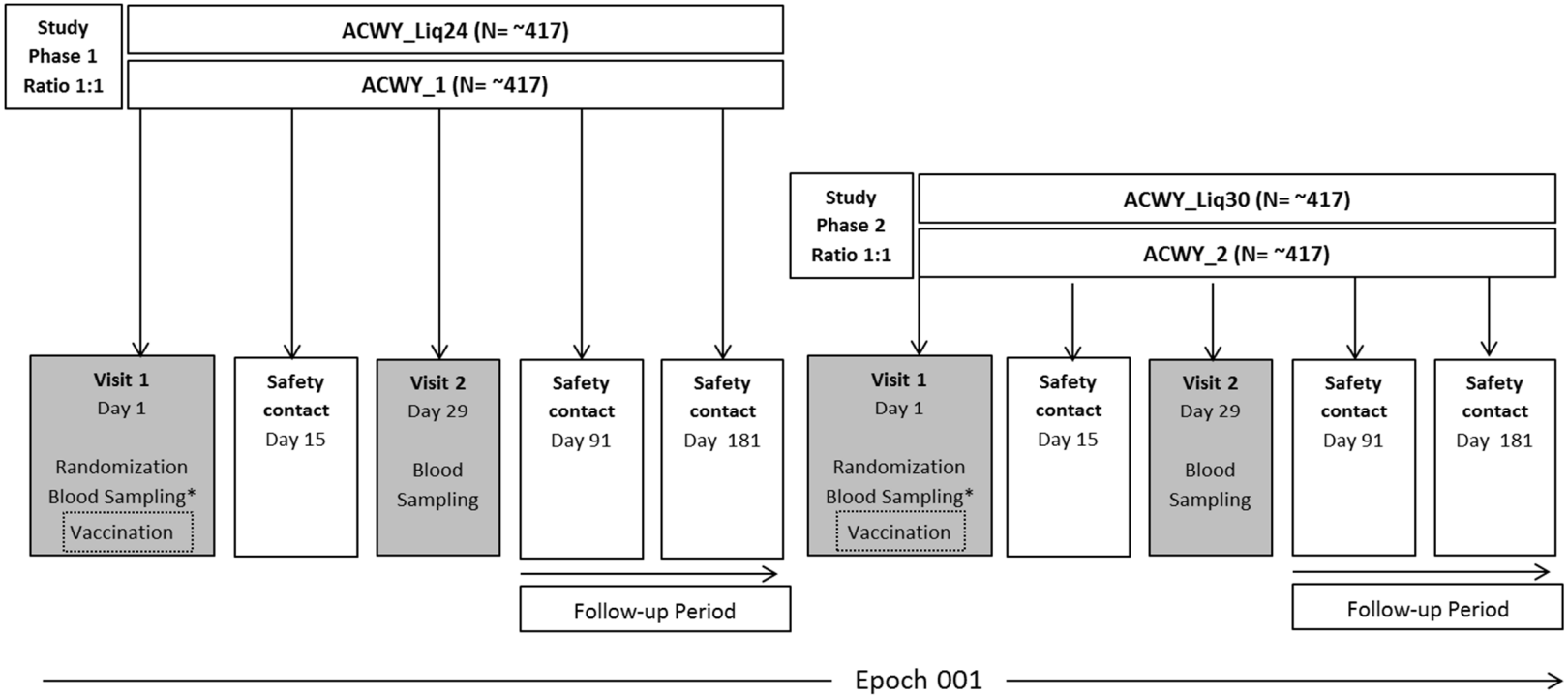
  Note: A 4-fold rise is defined as: a) for individuals whose pre-vaccination titers are < the limit of detection (LOD), the post-vaccination titers must be ≥ 4-fold the LOD or ≥ the lower limit of quantitation (LLOQ) whichever is greater; b) for individuals whose pre-vaccination titers are ≥ the LOD and ≤ the LLOQ, the post vaccination titers must be at least four times the LLOQ; and c) for individuals whose pre-vaccination titers are > the LLOQ, the post vaccination titers must be at least four times the pre-vaccination titer.
- To compare the immunogenicity of the investigational MenACWY liquid products aged for approximately 24 or 30 months and the currently licensed MenACWY vaccine, as measured by the percentage of subjects with hSBA titer ≥8 and ≥LLOQ* directed against *N. meningitidis* serogroups A, C, W and Y at Day 29.

  * Note: To be assessed for each serogroup if the pre-defined LLOQ value for that serogroup is >8.
- To assess the safety/reactogenicity of the investigational MenACWY liquid vaccine aged approximately 24 or 30 months and the currently licensed MenACWY vaccine.

Refer to Section 10.2 for the definition of the secondary endpoint(s).

# 3. STUDY DESIGN OVERVIEW

**Figure 1 Study design overview**




*Blood sample collection from Visit 1 will be performed before vaccine administration

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 5.5), are essential and required for study conduct.

- Experimental design: Phase IIB, observer-blind, randomized, controlled, multi-centric study with two parallel groups per phase, in a two phases staggered design.
- Duration of the study: The duration of this study is approximately 6 months per subject.
  - Epoch 001: starting at Visit 1 (Day 1) and ending at last Safety contact (Day 181).
- Primary completion Date (PCD): Visit 2 (Day 29).

  Refer to GLOSSARY OF TERMS for the definition of PCD.
- End of Study (EoS): Last subject last visit (Phone call 3) or last testing results released of samples collected at Visit 2 (Day 29) of Study Phase 2* if it occurs after LSLV.

  * In this case EoS must be achieved no later than 8 months after LSLV.

  Refer to GLOSSARY OF TERMS for the definition of EoS.
- Study groups:
  - **ACWY_Liq24** (Study Phase 1): approximately 417 healthy subjects receiving investigational MenACWY liquid vaccine (GSK3536820A) aged for approximately 24 months at 2-8oC;
  - **ACWY_1** (Study Phase 1): approximately 417 healthy subjects receiving currently licensed GSK' MenACWY vaccine (*Menveo*), not aged;
  - **ACWY_Liq30** (Study Phase 2): approximately 417 healthy subjects receiving investigational MenACWY liquid vaccine (GSK3536820A) aged for approximately 30 months at 2-8°C;
  - **ACWY_2** (Study Phase 2): approximately 417 healthy subjects receiving currently licensed GSK' MenACWY vaccine (*Menveo*), not aged.

**Table 1 Study groups and epochs foreseen in the study**

| Study groups | Number of subjects | Age (Min/Max) | Epochs |
|---|---|---|---|
| | | | Epoch 001 |
| ACWY_Liq24* | 417 | 10 years – 40 years | x |
| ACWY_1 | 417 | 10 years – 40 years | x |
| ACWY_Liq30** | 417 | 10 years – 40 years | x |
| ACWY_2 | 417 | 10 years – 40 years | x |

* ACWY_Liq24: vaccine lot aged for approximately 24 months.
** ACWY_Liq30: vaccine lot aged for approximately 30 months.

**Table 2 Study groups and treatment foreseen in the study**

| Treatment name | Vaccine/product name | Study Groups | | | |
|---|---|---|---|---|---|
| | | ACWY_Liq24 | ACWY_1 | ACWY_Liq30 | ACWY_2 |
| MenACWY liquid | MenACWY liquid | x | | x | |
| Licensed MenACWY (*Menveo**) | MenA lyo<br>MenCWY liquid | | x | | x |

* *Menveo* commercial formulation consisting of a MenA lyophilized component and of a MenCWY liquid component to be reconstituted together before administration.

- Control: active control.
- Vaccination schedule: All subjects will receive a single dose of study vaccine at Visit 1 (Day 1).
- Treatment allocation: Randomization will be performed at Visit 1 (Day 1) using a central randomization system on the internet (SBIR), with stratification to include 40% of subjects from ≥10 to <18 YoA and 60% from ≥18 to ≤40 YoA. Please refer to Section 5.2 for a detailed description of the randomization method.
- Blinding: observer-blind for each of the two phases of the study. Please refer to Section 5.3 for details of the blinding procedure.

**Table 3 Blinding of study epochs**

| Study Epochs | Blinding |
|---|---|
| Epoch 001 | observer-blind |

- Sampling schedule: Blood sample of approximately 20 ml will be collected from each subject at Visit 1 (Day 1; pre-vaccination) and at Visit 2 (Day 29).
- Type of study: self-contained.
- Data collection: Standardised Electronic Case Report Form (eCRF). Solicited adverse events (AEs) assessed on site during the 30 minutes post-vaccination assessment are to be recorded on the source documents and entered in the eCRF. Solicited AEs occurring after the 30 minutes post-vaccination assessment will be collected using a subject Diary (electronic Diary [eDiary]).

# 4. STUDY COHORT

## 4.1. Number of subjects

The target will be to enroll approximately 1668 subjects ≥10 to ≤40 YoA at the time of the vaccination (approximately 417 subjects per group). Assuming a 10% drop-out rate, there should be approximately 1500 evaluable subjects (approximately 375 evaluable subjects per group).

Please refer to Section 10.3 for a detailed description of the criteria used in the determination of sample size.

## 4.2. Inclusion criteria for enrollment

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity, regulatory acceptability of the study or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

All subjects must satisfy ALL the following criteria at study entry:

1. Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the eDiary) or subjects' parent(s)/Legally Acceptable Representative(s) [LAR(s)] who, in the opinion of the investigator, can and will comply, with the requirements of the protocol (e.g. completion of the eDiary).
2. Written informed consent obtained from the subject/from the parent(s)/LAR(s) of the subject prior to performing any study specific procedure.
3. Written informed assent obtained for subjects below legal age of consent, if required by local regulations at the time of the enrollment.
4. A male or female ≥10 to ≤40 YoA at the time of the vaccination.
5. Healthy subjects as established by medical history and clinical examination before entering into the study.
6. Female subjects of non-childbearing potential may be enrolled in the study.
   - Non-childbearing potential is defined as pre-menarche, current bilateral tubal ligation or occlusion, hysterectomy, bilateral ovariectomy or post-menopause

   Please refer to the GLOSSARY OF TERMSfor the definition of menarche and menopause.
7. Female subjects of childbearing potential may be enrolled in the study, if the subject:
   - has practiced adequate contraception for 30 days prior to vaccination, and
   - has a negative pregnancy test on the day of vaccination, and
   - has agreed to continue adequate contraception during the entire treatment period (1 month after vaccination)

   Please refer to the GLOSSARY OF TERMS for the definition of adequate contraception.

## 4.3. Exclusion criteria for enrollment

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity, regulatory acceptability of the study or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The following criteria should be checked at the time of study entry. If ANY exclusion criterion applies, the subject must not be included in the study:

1. Child in care

Please refer to the GLOSSARY OF TERMS for the definition of child in care.

Each subject must not have:

2. Anaphylaxis following the administration of vaccine.
3. Any (clinical) condition that in the judgment of the investigator would make intramuscular injection unsafe and/or represents a contraindication to intramuscular vaccination and blood draws.
4. Any confirmed or suspected immunosuppressive or immunodeficient condition, including HIV infection.
5. Progressive, unstable or uncontrolled clinical conditions.
6. Hypersensitivity, including allergy, to any component of vaccines, medicinal products or medical equipment whose use is foreseen in this study.
7. Hypersensitivity to the active substances or to any of the excipients of the vaccine, including diphtheria toxoid ($CRM_{197}$), or a life-threatening reaction after previous administration of a vaccine containing similar components.
8. Abnormal function of the immune system resulting from:
   - Clinical conditions.
   - Systemic administration of corticosteroids (PO/IV/IM) within 90 days prior to informed consent, and until the Day 29 blood draw.
   - Administration of antineoplastic and immunomodulating agents or radiotherapy within 90 days prior to informed consent, and until the Day 29 blood draw.
9. Received immunoglobulins or any blood products within 180 days prior to informed consent.
10. Received an investigational or non-registered medicinal product within 30 days prior to informed consent.
11. Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the subject due to participation in the study.
12. History of any meningococcal vaccination, with the exception of previous meningococcal C (conjugated or polysaccharide) vaccination, if the last dose of MenC was received at ≤24 months of age.
13. Individuals who received any other vaccines within 7 days (for inactivated vaccines) or 14 days (for live vaccines) prior to enrollment in this study or who are planning to receive any vaccine within 28 days from the study vaccines.*

    * In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is organized by the public health authorities, outside the routine immunization program, the time period described above can be reduced if necessary

for that vaccine provided it is licensed and used according to its Prescribing Information and according to the local governmental recommendations and provided a written approval of the sponsor is obtained.

14. Administration of long-acting immune-modifying drugs at any time during the study period (e.g. infliximab).
15. Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).
16. Current or previous, confirmed or suspected disease caused by *N. meningitidis*.
17. Household contact with and/or intimate exposure to an individual with any laboratory confirmed *N. meningitidis* infection within 60 days prior to study vaccination.
18. Acute disease and/or fever within 3 days prior to study vaccination.

    Note: enrollment may be postponed/delayed until such transient circumstances have ended.

    – Fever is defined as body temperature ≥38.0°C/100.4°F. The preferred location for measuring temperature in this study will be the oral cavity.
    – Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may be enrolled at the discretion of the investigator.
19. Received systemic antibiotic treatment within 3 days prior to study vaccination or blood draw.
20. Study personnel as an immediate family or household member.
21. Pregnant or lactating women. (see Section 8.2.1 for pregnancy)

# 5. CONDUCT OF THE STUDY

## 5.1. Regulatory and ethical considerations, including the informed consent process

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with the ICH Guideline for GCP, all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

The study has been designed and will be conducted in accordance with the ICH Harmonized Tripartite Guideline for clinical investigation of medicinal products in the paediatric population (ICH E11) and all other applicable ethical guidelines.

GSK will obtain favourable opinion/approval to conduct the study from the appropriate regulatory agency, in accordance with applicable regulatory requirements, prior to a site initiating the study in that country.

Conduct of the study includes, but is not limited to, the following:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject/ subject's parent(s)/LAR(s) informed consent and subject informed assent (if required by local regulations at the time of enrollment), as appropriate.
- Investigator reporting requirements as stated in the protocol.

GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.

Freely given and written or witnessed/ thumb printed informed consent must be obtained from each subject and/or each subject's parent(s)/LAR(s) and subject informed assent, as appropriate, prior to participation in the study.

GSK Biologicals will prepare a model Informed Consent Form (ICF) which will embody the ICH GCP and GSK Biologicals required elements. While it is strongly recommended that this model ICF is to be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgement, local regulations and requirements should guide the final structure and content of the local version of the ICF.

In accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, those subjects who can only be enrolled in the study with the consent of the subject's legally acceptable representative (e.g. minors), should be informed about the study to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date a written informed assent form (IAF). It is required that the assent be signed by each subject, if capable, in addition to the informed consent that is to be signed by his/her legal representative. It should be assessed whether an assent is required depending of the age of the study population and the local requirements.

GSK Biologicals strongly recommends that if the subject reaches the age of consent during the study they will be asked to provide consent at the next study visit (if applicable). This procedure should be applied according to local laws and regulations.

The investigator has the final responsibility for the final presentation of the ICF and IAF, respecting the mandatory requirements of local regulations. The ICF and IAF generated by the investigator with the assistance of the sponsor's representative must be acceptable to GSK Biologicals and be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC.

## 5.2. Subject identification and randomization

### 5.2.1. Subject identification

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.

### 5.2.2. Randomization of treatment

#### 5.2.2.1. Randomization of supplies

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

To allow GSK Biologicals to take advantage of greater rates of recruitment than anticipated at individual centers in this multi-center study and to thus reduce the overall study recruitment period, an over-randomization of supplies will be prepared.

#### 5.2.2.2. Treatment allocation to the subject

The treatment numbers will be allocated by dose.

##### *5.2.2.2.1. Study group and treatment number allocation*

The target will be to enrol approximately 1668 eligible subjects (≥10 to ≤40 YoA) who will be randomly assigned to four study groups: two study groups in a (1: 1) ratio for study phase 1, and two study groups in a (1: 1) ratio for study phase 2 (i.e. approximately 417 subjects in each group per phase).

The enrollment will be performed to ensure the following distribution across the two age strata: 40% of subjects from ≥10 to <18 YoA and 60% from ≥18 to ≤40 YoA. Therefore the expected distribution of subjects is as shown in Table 4.

**Table 4 Number of subjects required for enrollment**

| Age Stratum | Study Group | N |
|---|---|---|
| ≥10 to <18 years | ACWY_Liq24 (Study Phase 1) | 167 |
| | ACWY_1 (Study Phase 1) | 167 |
| | ACWY_Liq30 (Study Phase 2) | 167 |
| | ACWY_2 (Study Phase 2) | 167 |
| ≥18 to ≤40 years | ACWY_Liq24 (Study Phase 1) | 250 |
| | ACWY_1 (Study Phase 1) | 250 |
| | ACWY_Liq30 (Study Phase 2) | 250 |
| | ACWY_2 (Study Phase 2) | 250 |

N = approximate number of subjects to be enrolled

Allocation of the subject to a study group at the investigator site will be performed using the Source DataBase for Internet Randomization system (SBIR). Within each age stratum (≥10 to <18 YoA versus ≥18 to ≤40 YoA), the randomization algorithm will use a minimization procedure accounting for center.

After obtaining the signed and dated ICF/IAF from the subject and having checked the eligibility of the subject, the study staff in charge of the vaccine administration will access SBIR. Upon providing the age (≥10 to <18 YoA versus ≥18 to ≤40 YoA) and the subject identification number, the randomization system will determine the study group and will provide the treatment number to be used for the dose.

The number of each administered treatment must be recorded in the eCRF on the Vaccine Administration screen.

When SBIR is not available, please refer to the SBIR user guide or the Study Procedures Manual (SPM) for specific instructions.

Note that as soon as the target number of subjects in a specific age group has been reached, the enrollment will be frozen for this age group.

## 5.3. Method of blinding (Amended 08 February 2019)

Data will be collected in an observer-blind manner. By observer-blind, it is meant that during the course of the study, the vaccine recipient and those responsible for the evaluation of any study endpoint (e.g. safety, reactogenicity) will all be unaware of which vaccine was administered. To do so, vaccine preparation and administration will be done by authorized medical personnel who will not participate in any of the study clinical evaluation assays.

The laboratory in charge of the laboratory testing will be blinded to the treatment ***as well as to the*** subject number. ***In addition, a randomly selected subject code will be used for each timepoint tested. This subject coding will prevent the laboratory from linking the consecutive visits to a specific subject***.

## 5.4. General study aspects

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying SPM. The SPM provides the investigator and the site personnel with administrative and detailed technical information that does not impact the safety of the subjects.

## 5.5. Outline of study procedures

### Table 5 List of study procedures

| Age | ≥10 to ≤40 YoA | | | | |
|---|---|---|---|---|---|
| Epoch | Epoch 001 | | | | |
| Type of contact | Visit 1 | Phone call 1 | Visit 2 | Phone call 2 | Phone call 3 |
| Timepoint (s) | Day 1 | Day 15 | Day 29 | Day 91 | Day 181 |
| Sampling timepoint(s) | Pre-Vacc | | Post-Vacc | | |
| Informed consent | ●[a] | | | | |
| Informed assent (if applicable as per local regulations) | ●[a] | | | | |
| Check inclusion/exclusion criteria | ●[a] | | | | |
| Collect demographic data | ●[a] | | | | |
| Medical history | ●[a] | | | | |
| Physical examination (including vital signs) | ● | | ●[b] | | |
| Urine pregnancy test [c] | ● | | | | |
| Check contraindications and warnings and precautions to vaccination | O | | | | |
| Pre-vaccination body temperature | ● | | | | |
| Measure/record height and weight | ●[a] | | | | |
| Study group and treatment number allocation | ● | | | | |
| Recording of administered treatment number | ● | | | | |
| Blood sampling (approximately 20 mL) [d] | ●[e] | | ● | | |
| Vaccine administration | ● | | | | |
| 30 Minutes post Injection Assessment | ● | | | | |
| Distribution of Subject Card | O[a] | | | | |
| Distribution of eDiary | O | | | | |
| Training on use of eDiary | O | | | | |
| Return of eDiary | | | O | | |
| Record any concomitant medications/vaccinations | ● | ● | ● | | |
| Record concomitant medications/vaccinations related to SAEs, AEs/SAEs leading to study withdrawals and to medically attended visits | ● | ● | ● | ● | ● |
| Record any intercurrent medical conditions | ● | ● | ● | ● | ● |
| Recording of solicited adverse events (Days 1-7 post-vaccination in eDiary) | ● | | | | |
| Recording of unsolicited adverse events within 28 days post-vaccination | ● | ● | ● | | |
| Recording of medically-attended AEs | ● | ● | ● | ●[f] | ●[f] |
| Recording of AEs/SAEs leading to withdrawal | ●[a] | ● | ● | ● | ● |
| Recording of SAEs | ● | ● | ● | ● | ● |
| Recording of pregnancies | ● | ● | ● | ● | ● |
| Study Conclusion | | | | | ● |

Note: The double-line border following Day 29 indicates the interim analysis which will be performed on all data obtained up to Day 29 for phase 1 of the study.
AE = adverse event; GSK = GlaxoSmithKline; SAE = severe adverse event; Vacc: vaccination; YOA = years of age
● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF, but should be confirmed in the patient's source record.
[a]The following activities can be performed as a separated visit before Visit 1 (maximum 5 days before the Visit 1): Informed Consent, ***Informed Assent,*** check of inclusion/exclusion criteria, collection of demographic data, recording of Medical History and of height and weight, distribution of Subject Card . AEs leading to withdrawals and AEs/ SAEs

related to study participation or to a concurrent GSK medication/vaccine should also be recorded from this separated visit. Inclusion/exclusion criteria should be re-checked prior to vaccination.
[b] Physical examination will be performed only if deemed necessary by the Investigator or delegate.
[c] Only for women of childbearing potential.
[d] Before blood sample collection, check if there is no contraindication to blood draw.
[e] Blood sample collection from Visit 1 will be performed before vaccine administration.
[f] Non-medically attended AEs after 28 days post-vaccination are not required to be reported in the eCRF.

Whenever possible, the investigator should arrange study visits within the interval described in Table 6.

**Table 6 Intervals between study visits**

| Interval | Optimal length of interval | Allowed interval |
|---|---|---|
| Visit 1 → Phone call 1 | 14 days | 11 - 17 days |
| Visit 1 → Visit 2 | 28 days | 21 - 42 days |
| Visit 1 → Phone call 2 | 90 days | 76 - 104 days |
| Visit 1 → Phone call 3 | 180 days | 166 - 194 days |

## 5.6. Detailed description of study procedures

### 5.6.1. Informed consent

The signed/witnessed/thumb printed informed consent of the subject/subject's parent(s)/LAR(s) must be obtained before study participation. The signed informed assent of the subject below the age of consent (i.e. minor) should be obtained in addition to the signed informed consent by his/her parent(s)/LAR(s) according to local rules and regulations. Refer to Section 5.1 for the requirements on how to obtain informed consent and assent, as appropriate.

### 5.6.2. Check inclusion and exclusion criteria

Check all inclusion and exclusion criteria as described in Sections 4.2 and Section 4.3 before enrollment.

### 5.6.3. Collect demographic data

Record demographic data such as year of birth, sex, race and ethnicity in the subject's eCRF.

Differences in the safety and efficacy of certain medical products, including vaccines [Haralambieva, 2013; Pérez-Losada, 2009; Kollmann, 2013], have been observed in racially and ethnically distinct subgroups. These differences may be attributable to intrinsic factors (e.g. genetics, metabolism, elimination), extrinsic factors (e.g. diet, environmental exposure, sociocultural issues), or interactions between these factors. Therefore, both race and ethnicity will be collected for all subjects participating in the MENACWY CONJ-069 [V59_78] study. Subgroup analysis by race will be performed.

### 5.6.4. Medical history

Obtain the subject's medical history by interview and/or review of the subject's medical records and record any pre-existing conditions or signs and/or symptoms present in a subject prior to the study vaccination in the eCRF.

### 5.6.5. Physical examination

Review of systems is a structured interview that queries the subject as to any complaints the subject has experienced across each organ system. This will be performed before enrollment and used to guide physical examination. Collect vital signs (heart rate, blood pressure), and temperature (preferably taken orally). Measure height and weight. 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 (or alternatively called Delegation of Responsibilities Log). The data collected through study assessments listed above will be written in the source document. Should the physical assessment reveal any abnormal values or events, these must be documented in the CRF Adverse Events Form. Collected information needs to be recorded in the eCRF.

Physical examination at each study visit subsequent to the vaccination visit, will be performed only if the subject indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the Investigator or delegate.

If the investigator determines that the subject's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled.

Treatment of any abnormality observed during physical examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

### 5.6.6. Urine Pregnancy test

Female subjects of childbearing potential are to have a urine pregnancy test prior to any study vaccine administration. The study vaccine may only be administered if the pregnancy test is negative.

Note: Pregnancy test must be performed even if the subject is menstruating at the time of the study visit.

Pregnancy test should also be performed for minor female subjects if the subject meets criteria of childbearing potential, according to the Investigator.

### 5.6.7. Check contraindications, warnings and precautions to vaccination

Contraindications, warnings and precautions to vaccination must be checked at the beginning of the vaccination visit. Refer to Section 6.5 and Section 6.6 for more details.

### 5.6.8. Assess pre-vaccination body temperature

The oral body temperature of each subject needs to be measured prior to any study vaccine administration. If the subject has fever (fever is defined as body temperature ≥38.0°C/100.4°F regardless the location of measurement) on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Table 6).

### 5.6.9. Measure/record height and weight

Measure height and weight of the subject and record the data in the 'Physical examination' section of the eCRF.

### 5.6.10. Study group and treatment number allocation

Study group and treatment number allocation will be performed as described in Section 5.2.2. The number of each administered treatment must be recorded in the eCRF.

### 5.6.11. Sampling

Refer to the Module on Biospecimen Management in the SPM and the Central Laboratory Manual for detailed instructions for the collection, handling and processing of the samples.

#### 5.6.11.1. Blood sampling for immune response assessments

Blood samples will be taken during certain study visits as specified in Table 5 (List of Study Procedures).

- A volume of approximately 20 mL of whole blood should be drawn from all subjects for each analysis of humoral immune response at each pre-defined timepoint (Visit 1 and Visit 2). After centrifugation, serum samples should be kept at –20°C/-4°F or below until shipment. Refer to the SPM or Central Laboratory Manual for more details on sample storage conditions.
- An overall volume of approximately 40 mL will be collected during the entire study period.

### 5.6.12. Study Vaccine administration

- After completing all prerequisite procedures prior to vaccination, one dose of study vaccine will be administered intramuscularly (IM) in the deltoid of the non-dominant arm (refer to Section 6.3 for detailed description of the vaccine administration procedure). If the investigator or delegate determines that the subject's health on the day of administration temporarily precludes vaccine administration, the visit will be rescheduled within the allowed interval for this visit (refer to Table 6).
- The subjects will be observed closely for at least 30 minutes following the administration of the vaccines, with appropriate medical treatment readily available in case of anaphylaxis.

### 5.6.13. Distribution of Subject Card

For information regarding the Subject Card, please refer to Section 8.9.

### 5.6.14. Subject Diary

An Electronic Diary (eDiary), hereafter referred to as Subject Diary will be used in this study to capture solicited adverse events. The subject should be trained on how and when to complete each field of 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/subject's parent(s)/LAR(s), but if a person other than the subject/subject's parent(s)/LAR(s) enters information into the Subject Diary, this person's identity must be documented in the 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 when Subject Diary is dispensed. 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 subject/subject's parent(s)/LAR(s) should be trained on how to self-measure local solicited adverse events and body temperature.

The measurement of solicited local adverse events is to be performed using the ruler provided by the site.

Subjects/parents/LARs will be instructed to measure and record the oral body temperature in the evening. Should additional temperature measurements be performed at other times of day, subjects/parents/LARs will be instructed to record the highest temperature in the Subject Diary.

Subject Diary assignment and use:

- Each subject/subject's parent(s)/LAR(s) will be assigned a Subject Diary and shown how to use the device – this will include how to access the diary, performing test data entry on sample questions, and how to charge and store the device.
- The subject/subject's parent(s)/LAR(s) will self-select a numeric access code secret to themselves. The same individual should make the assessments and complete the Subject Diary throughout the course of the study.
- The subject/subject's parent(s)/LAR(s) will select an alarm time that suits their daily routines whilst ensuring compliance with protocol requirements.

Subject Diary instructions must ensure that the subject/subject's parent(s)/LAR(s) understands the following:

- Timely completion of the Subject Diary on a daily basis is a critical component to study participation.
- The Subject Diary will allow certain time windows for completion of each day's observations.
- The Subject Diary employs the use of audio-visual alarms to ensure timely completion of data entry.
- The trained and assigned user of the Subject Diary must not share access codes with anyone.
- A helpdesk will be provisioned for users of subject diary in case of technical issues, though it must be stressed that the Helpdesk is not a replacement for normal medical care and no medical issues can be discussed with the agents.
- The Subject Diary itself must never be considered a substitute for direct medical care and any concerns must be communicated to site staff as soon as possible.

#### 5.6.14.1. Post-vaccination reminders

Reminder calls or alerts are not intended to be an interview for collection of safety data. If the subject/subject's parent(s)/LAR(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.

##### *5.6.14.1.1. Subject Diary Reminder Alerts*

The subject/subject's parent(s)/LAR(s) will receive daily reminders via the Subject Diary device's in-built audio-visual alarms to alert the user to complete the diary during the post vaccination period. From Day 1 through Day 7, the users will receive daily alerts through the Subject Diary to record solicited adverse events, and the incidence of any potential unsolicited AEs, and whether these AEs were 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. In case of such events, subjects/subjects' parents/LARs will be instructed to contact the site as soon as possible to report the event(s).

The Subject Diary system will also allow for regular alerts to be issued via email to site staff indicating where subjects may need to be contacted due to:

- Non-compliance (i.e. failing to enter or transmit diary data),
- Reporting of any severe solicited reactions,
- Subject experienced an unsolicited adverse event that was medically attended or was of concern.

Sites must assess these alerts when received and contact subjects as necessary. Please refer to Section 9.2 on the premature withdrawals from the study and Section 8.3.3 on the evaluation of Adverse Events for guidance on necessary action in the event of one of these alerts.

#### 5.6.14.2. Safety Follow-up calls

Safety follow-up calls will be performed on Day 15, Day 91, and day 181 (or within the allowed interval specified in Table 6).

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/subject's parent(s)/LAR(s) will be interviewed according to the script, and information relating to unsolicited adverse events (including unsolicited adverse events [AEs] within 28 days post-vaccination, serious adverse events [SAEs], medically attended adverse events, AEs leading to withdrawal, and/or intercurrent medical conditions) and concomitant medications or vaccinations associated with those events will be collected, as well as information on pregnancy for females of child-bearing potential. All safety information described by the subject must be written down in a designated location within the source document and not written on the script used for the telephone call.

The site should schedule the next study activity (clinic visit/ safety call) with the subject/subject's parent(s)/LAR(s).

The subject/subject's parent(s)/LAR(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.

### 5.6.15. Check and record concomitant medication/vaccination and intercurrent medical conditions

Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 6.7.

Intercurrent medical conditions must be checked and recorded in the eCRF as described in Section 6.8.

### 5.6.16. Recording of AEs, SAEs and pregnancies

- Refer to Section 8.3 for procedures for the investigator to record AEs, SAEs and pregnancies. Refer to Section 8.4 for guidelines and how to report SAE and pregnancy reports to GSK Biologicals.
- The subjects/subjects' parents/LARs will be instructed to contact the investigator immediately should they/the subjects manifest any signs or symptoms they perceive as serious.

### 5.6.17. Study conclusion

The investigator will:

- review data collected to ensure accuracy and completeness
- complete the Study Conclusion screen in the eCRF.

## 5.7. Biological sample handling and analysis

Please refer to the SPM or Central Laboratory Manual for details on biospecimen management (handling, storage and shipment).

Samples will not be labelled with information that directly identifies the subject but will be coded with a unique sample identifier.

- Collected samples will be used 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 allowed will be asked to give a specific consent to allow GSK or a contracted partner to use the samples for future research. Future research will be subject to the laws and regulations in the respective countries and will only 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 Biologicals.

Any sample testing will be done in line with the consent of the individual subject/subject's parent(s)/LAR(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).

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 Biologicals.

### 5.7.1. Use of specified study materials

When materials are provided by GSK Biologicals or designated vendor, it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the per-protocol analysis (See Section 10.4 for the definition of analysis sets to be analysed). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals or designated vendor does not provide material for collecting and storing clinical samples, appropriate materials from the investigator's site must be used. Refer to the Module on Clinical Trial Supplies in the SPM or Central Laboratory Manual.

### 5.7.2. Biological samples

**Table 7 Biological samples**

| Sample type | Quantity | Unit | Timepoint |
|---|---|---|---|
| Blood | Approximately 20 | ml | • Visit 1 (Day 1)<br>• Visit 2 (Day 29) |

### 5.7.3. Laboratory assays (Amended 08 February 2019)

Please refer to APPENDIX A for a detailed description of the assays performed in the study. Please refer to APPENDIX B for the address of the clinical laboratories used for sample analysis.

The measures of immunogenicity 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 immune response). Testing will be conducted by a GSK or designated laboratory in a blinded manner towards the subject number ***and*** the treatment arm ***(please refer to Section 5.3 Method of blinding)***.

The functional measure of immunogenicity used in this study, Serum Bactericidal Assay (SBA), is a measure of the ability of antibodies, mediated with human complement, to kill meningococci, and is widely used and generally recognized as the serological correlate of protection.

**Table 8 Humoral Immunity (Antibody determination)**

| System | Component | Method | Kit / Manufacturer | Unit* | Cut-off* | Laboratory |
|---|---|---|---|---|---|---|
| Humoral | *Neisseria meningitidis* serogroup A | Serum Bactericidal Assay, using human complement | In house | 1/Dilution | TBD | GSK Biologicals** or a laboratory designated by GSK Biologicals |
| | *Neisseria meningitidis* serogroup C | | | | | |
| | *Neisseria meningitidis* serogroup W | | | | | |
| | *Neisseria meningitidis* serogroup Y | | | | | |

TBD = To be determined.
* For each of the indicator strains to be used in hSBA assays, assay cut-off and unit will be determined following validation of the selected MenACWY hSBA format. This will be documented in the clinical report.
** GSK Biologicals refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium; Marburg, Germany.

Additional exploratory testing on the vaccine and/or on the disease under study may be performed within the framework of the study if deemed necessary for accurate interpretation of the data or should such assay(s) become available at GSK. These assays may not be represented in the objectives/endpoints of the study protocol.

The GSK Biologicals' clinical laboratories have established a Quality System supported by procedures. The activities of GSK Biologicals' clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department.

## 5.7.4. Biological samples evaluation

### 5.7.4.1. Immunological read-outs

**Table 9 Immunological read-outs**

| Blood sampling timepoint | | No. subjects (planned) | Component | Components priority rank |
|---|---|---|---|---|
| Type of contact and timepoint | Sampling timepoint | | | |
| Visit 1 (Day 1) | Pre-Vacc | ~1668 | hSBA | MenA > MenC = MenY > MenW |
| Visit 2 (Day 29) | Post-Vacc | ~1668 | hSBA | MenA > MenC = MenY > MenW |

hSBA = human serum bactericidal assay

### 5.7.5. Immunological correlates of protection

Although a hSBA titer ≥4 is an accepted correlate of protection against invasive meningococcal disease caused by the C serogroup, GSK Biologicals has historically used a more stringent immunological correlate (hSBA titer ≥8) for the definition of seroprotection against *N. menigitidis*.

Seropositivity cut-off or other hSBA titer values used to support definitions for a 4-fold rise in titers may change following the generation of additional qualification/validation data as expected by Center for Biologics Evaluation and Research (CBER) to support the intended use of the MenACWY hSBAs. The values of LLOQ and LOD for each serogroup will be defined at the time of the generation of qualification and/or validation data.

The clinical endpoints used in this study are standard measures used routinely to estimate protection against meningococcal disease and have been previously agreed with CBER in the frame of *Menveo* licensure. The anticipated margin of the GMT ratio (lower limit of 0.5 for the 95% CI of the GMT ratios between groups) for study success has previously been used in the demonstration of lot-to-lot consistency in pivotal *Menveo* trials in adolescents.

The investigator is encouraged to share the immunological assay results for non-responders with the study subjects/subjects' parents/LARs at the end of the study, as soon as the results are available**.**

For the subjects identified as non-responders, it remains the responsibility of the investigator in charge of the subject's clinical management to determine the medical need for re-vaccination and to re-vaccinate the subjects as per local/regional practices. Subjects who do not achieve a ≥ 4-fold rise in hSBA titers (according to the definition in the objectives) against any of the 4 serogroups at 1 month post-vaccination with the investigational MenACWY liquid vaccine will be offered one dose of a licensed quadrivalent MenACWY vaccine (preferable *Menveo*) after the end of the study and outside study procedures.

# 6. STUDY VACCINES AND ADMINISTRATION

## 6.1. Description of study vaccines

All candidate vaccines to be used have been developed and manufactured by GSK Biologicals.

The Quality Control Standards and Requirements for the candidate vaccine are described in separate Quality Assurance documents (e.g. release protocols, certificate of analysis) and the required approvals have been obtained.

The vaccines are labelled and packed according to applicable regulatory requirements.

Commercial vaccine is assumed to comply with the specifications given in the manufacturer's Summary of Product Characteristics.

**Table 10 Study vaccines**

| Treatment name | Vaccine/product name | Formulation | Presentation | Volume to be administered | Number of doses |
|---|---|---|---|---|---|
| MenACWY liquid | MenACWY liquid | MenA=10µg CRM197; MenC=5µg CRM197; MenW=5µg CRM197; MenY=5µg CRM197; CRM197=25.4-65.8µg | Liquid in a monodose vial | 0.5 ML | 1 |
| Licensed MenACWY *(Menveo*)* | MenA lyo | MenA=10µg CRM197; CRM197=16.7-33.3µg | Lyophilized component in a vial | 0.5 ML | 1 |
| | MenCWY liquid | MenC=5µg CRM197; MenW=5µg CRM197; MenY=5µg CRM197; CRM197=16-30.8µg | Liquid component in a vial | | |

* *Menveo* commercial formulation consisting of a MenA lyophilized component and of a MenCWY liquid component to be reconstituted together before administration (0.5 mL)

## 6.2. Storage and handling of study vaccines

The study vaccines must be stored at the respective label storage temperature conditions in a safe and locked place. Access to the storage space should be limited to authorized study personnel. The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded. Refer to the Module on Clinical Trial Supplies in the SPM for more details on storage of the study vaccines.

Temperature excursions must be reported in degree Celsius.

Any temperature excursion outside the range of 2.0 to +8.0°C (for +2 to +8°C / +36 to 46°F label storage condition) impacting investigational medicinal products (IMPs) must be reported in the appropriate (electronic) temperature excursion decision form (Advanced Temperature Excursion Analysis and Management [ATEAM]). The impacted IMPs must not be used and must be stored in quarantine at label temperature conditions until usage approval has been obtained from the sponsor.

Non-IMPs that are impacted by a temperature excursion may not be used and must be quarantined at label storage conditions until usage approval has been obtained from/via the local study contact (e.g. Site Monitor). There is no need for reporting via the (e)TDF.

Refer to the Module on Clinical Trial Supplies in the SPM for details and instructions on the temperature excursion reporting and usage decision process, packaging and accountability of the study vaccines.

## 6.3. Dosage and administration of study vaccines

**Table 11 Dosage and administration**

| Type of contact and timepoint | Study group | Treatment name | Volume to be administered | Route[1] | Site | |
|---|---|---|---|---|---|---|
| | | | | | Location | Laterality[2] |
| Visit 1 (Day 1) | ACWY_Liq24 | MenACWY liquid | 0.5 ml | IM | Deltoid | Non-dominant |
| | ACWY_Liq30 | | | | | |
| | ACWY_1 | Licensed MenACWY (*Menveo**) | 0.5 ml | IM | Deltoid | Non-dominant |
| | ACWY_2 | | | | | |

[1] Intramuscular (IM)
[2] The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the vaccine in the non-dominant arm, an injection in the dominant arm may be performed.
* *Menveo* commercial formulation consisting of a MenA lyophilized component and of a MenCWY liquid component to be reconstituted together before administration. Please refer to the SPM for the preparation methods.

## 6.4. Replacement of unusable vaccine doses

In addition to the vaccine doses provided for the planned number of subjects (including over-randomization when applicable), at least 30% additional vaccine doses will be supplied to replace those that are unusable.

The investigator will use SBIR to obtain the replacement vial number. The replacement numbers will be allocated by dose. The system will ensure, in a blinded manner, that the replacement vial matches the formulation the subject was assigned to by randomization.

## 6.5. Contraindications to vaccination

The following events constitute contraindications to administration of the investigational MenACWY liquid vaccine and the licensed MenACWY vaccine at that point in time; if any of these events occur at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol (see Table 6), or the subject may be withdrawn at the discretion of the investigator (see Section 8.5).

- Acute disease and/or fever within 3 days prior to study vaccination.
  - Fever is defined as body temperature ≥ 38.0°C/100.4°F. The preferred location for measuring temperature in this study will be the oral cavity.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever can be administered all vaccines.

## 6.6. Warnings and precautions

Refer to the approved product label/package insert for *Menveo*.

## 6.7. Concomitant medications/products and concomitant vaccinations

At each study visit/contact, the investigator or delegate should question the subject and/or the subject's parent(s)/LAR(s) about any medications/products taken and vaccinations received by the subject.

### 6.7.1. Recording of concomitant medications/products and concomitant vaccinations

The following concomitant medication(s)/product(s)/vaccine(s) must be recorded in the eCRF.

- All concomitant medications/products, except vitamins and dietary supplements, administered during the period of 28 days following the dose of study vaccine (Day 1 to Day 29).
- Any concomitant vaccination administered in the period starting 14 days before the dose of study vaccine and ending at the last study visit (Day -14 to Day 29).
- Prophylactic medication (i.e. medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).

  E.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring (fever is defined as body temperature ≥ 38.0°C/100.4°F regardless the location of measurement). The preferred location for measuring temperature in this study will be the oral cavity.
- Any concomitant medications/products/vaccines listed in Section 6.7.2.
- During the follow-up period, after Day 29 until the last safety phone call, any concomitant medications/products/vaccines relevant to a SAE, an AE/SAE leading to withdrawal or to an AE requiring a medically attended visit to be reported as per protocol. In addition, concomitant medications relevant to SAEs need to be recorded on the expedited Adverse Event report.
- Any antipyretic administered in the period starting 6 hours before vaccination and ending 12 hours after vaccination need to be recorded on the specific page of the eCRF.

### 6.7.2. Concomitant medications/products/vaccines that may lead to the elimination of a subject from per-protocol analyses

The use of the following concomitant medications/products/vaccines will not require withdrawal of the subject from the study but may determine a subject's evaluability in the per-protocol analysis. See Section 10.4 for analyses sets to be analysed.

- Any investigational or non-registered product (drug or vaccine) other than the study vaccine used during the study period.
- Immunosuppressants or other immune-modifying drugs defined as follows:
  - Systemic administration of corticosteroids (PO/IV/IM) within 90 days prior to informed consent, and until the Day 29 blood draw.
  - Administration of antineoplastic and immuno-modulating agents or radiotherapy within 90 days prior to informed consent.
- Long-acting immune-modifying drugs administered at any time during the study period (e.g. infliximab), and until the Day 29 blood draw.
- Other vaccines within 7 days (for inactivated vaccines) or 14 days (for live vaccines) prior to enrollment in this study or who are planning to receive any vaccine within 28 days of receiving the study vaccines*.

  * In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is organized by the public health authorities, outside the routine immunization program, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to its Prescribing Information and according to the local governmental recommendations and provided a written approval of the sponsor is obtained.
- Immunoglobulins and/or any blood products administered during the study period.
- Systemic antibiotics within 3 days prior to any blood draw.

## 6.8. Intercurrent medical conditions that may lead to elimination of a subject from per-protocol analyses

At each study visit/phone call subsequent to the vaccination visit, it must be verified if the subject has experienced or is experiencing any intercurrent medical condition. If it is the case, the condition(s) must be recorded in the eCRF.

Subjects may be eliminated from the per-protocol set for immunogenicity if, during the study period up to Day 29, they incur a condition that has the capability of altering their immune response (i.e. confirmed immunosuppressive or immunodeficient condition, including HIV) or are confirmed to have an alteration of their initial immune status.

# 7. HEALTH ECONOMICS

Not applicable.

# 8. SAFETY

The investigator or site staff is/are responsible for the detection, documentation and reporting of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE) as provided in this protocol.

Each subject/subject's parent(s)/LAR(s) will be instructed to contact the investigator immediately should they/the subject manifest any signs or symptoms they perceive as serious.

## 8.1. Safety definitions

### 8.1.1. Definition of an adverse event

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study vaccine administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study vaccine or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with study vaccine administration.
- Significant failure of expected pharmacological or biological action.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).

AEs to be recorded as endpoints (solicited AEs) are described in Section 8.1.3. All other AEs will be recorded as UNSOLICITED AEs.

Examples of an AE DO NOT include:

- Medical or surgical procedures (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE/SAE.

- Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Pre-existing conditions or signs and/or symptoms present in a subject prior to the study vaccination. These events will be recorded in the medical history section of the eCRF.

### 8.1.2. Definition of a serious adverse event

A SAE is any untoward medical occurrence that:

a. Results in death,

b. Is life-threatening,

   Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

c. Requires hospitalization or prolongation of existing hospitalization,

   Note: In general, hospitalization signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting. Complications that occur during hospitalization are also considered AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

   Hospitalization for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AE.

d. Results in disability/incapacity, OR

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

e. Is a congenital anomaly/birth defect in the offspring of a study subject.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

### 8.1.3. 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 subjects/parents/LARs for 7 consecutive days (6 hours – Day 7), using a pre-defined Subject Diary. Solicited adverse events continuing beyond Day 7 should continue to be recorded in the eDiary until resolution or the next visit.

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:

#### 8.1.3.1. Solicited Local Adverse Events

- Induration at injection site
- Erythema at injection site
- Pain at injection site

#### 8.1.3.2. Solicited Systemic Adverse Events

- Fever (body temperature ≥38.0°C/100.4°F)
- Chills
- Nausea
- Myalgia
- Arthralgia
- Headache
- Fatigue
- Loss of appetite

The preferred location for measuring temperature in this study will be the oral cavity.

#### 8.1.3.3. Other Solicited Adverse Events

Other indicators of reactogenicity:

- Use of analgesics / antipyretics for treatment;
- Use of analgesics / antipyretics for prophylaxis;

The study staff must review the data entered into the Subject Diary as described in Section 11.2.

Note: Any solicited adverse event that meets any of the following criteria must be entered into subjects' source document (see Section 11.2) and also as an adverse event on the Adverse Event CRF:

- Solicited local or systemic adverse event that leads to a visit to a healthcare provider (medically attended adverse event, see Section 8.3.3.4).
- 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).
- Solicited local or systemic adverse event that otherwise meets the definition of a serious adverse event (see Section 8.1.2).

### 8.1.4. Unsolicited Adverse Events

An unsolicited adverse event is an adverse event that was not solicited using a Subject Diary and that was spontaneously communicated by a subject/parent(s)/LAR(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 subjects/parents/LARs. In case of such events, subjects/parents/LARs will be instructed to contact the site as soon as possible to report the event(s). The detailed information about the reported unsolicited AEs will be collected by the qualified site personnel during the interview and will be documented in the subject's records.

Unsolicited AEs that are not medically attended nor perceived as a concern by subjects/parents/LARs will be collected during interview with the subjects/parents/LARs and by review of available medical records at the next visit.

### 8.1.5. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

In absence of diagnosis, abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g. clinical signs, ECG, radiological or diagnostic assessments) that are judged by the investigator to be clinically significant will be recorded as AE or SAE if they meet the definition of an AE or SAE (refer to Section 8.1.1 and Section 8.1.2). Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

## 8.2. Events or outcomes not qualifying as adverse events or serious adverse events

### 8.2.1. Pregnancy

Female subjects who become pregnant after the vaccination may continue the study at the discretion of the investigator.

While pregnancy itself is not considered an AE or SAE, any adverse pregnancy outcome or complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an AE or a SAE.

Note: The pregnancy itself should always be recorded on an electronic pregnancy report.

The following should always be considered as SAE and will be reported as described in Section 8.4.1 and Section 8.4.3:

- Spontaneous pregnancy loss, including:
  - spontaneous abortion, (spontaneous pregnancy loss before/at 22 weeks of gestation)
  - ectopic and molar pregnancy
  - stillbirth (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 [EMA, 2006]. 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 [CDC MACDP] 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.

Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered by the investigator to be reasonably related to the study vaccines will be reported to GSK Biologicals as described in Section 8.4.3. While the investigator is not obligated to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.

## 8.3. Detecting and recording adverse events, serious adverse events and pregnancies

### 8.3.1. Time period for detecting and recording adverse events, serious adverse events and pregnancies

All AEs starting within 28 days following administration of the dose of study vaccine (Day 1 to Day 29) must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

The time period for collecting and recording SAEs, AEs/SAEs leading to withdrawal from the study, and medically-attended AEs and SAEs will begin at the receipt of study vaccine and will end 180 days following administration of the dose of study vaccine for each subject (at the contact at Day 181). See Section 8.4 for instructions on reporting of SAEs.

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of receipt of study vaccine.

In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs that are related to study participation (i.e. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged from the study.

The time period for collecting and recording pregnancies will begin at the receipt of study vaccine and will end 180 days following administration of the dose of study vaccine (at the contact at Day 181). See section 8.4 for instructions on reporting of pregnancies.

An overview of the protocol-required reporting periods for AEs, SAEs, and pregnancies is given in Table 12.

**Table 12 Reporting periods for collecting safety information**

| | V1 | | Phone call 1 | V2 | Phone call 2 | Phone call 3 Study Conclusion |
|---|---|---|---|---|---|---|
| | D1 | D7 | D15 | D29 | D91 | D181 |
| Solicited local and systemic AEs | | | | | | |
| Unsolicited AEs | | | | | | |
| AEs/SAEs leading to withdrawal from the study | | | | | | |
| Medically-attended AEs, SAEs | | | | | | |
| SAEs related to the study vaccine | | | | | | |
| SAEs related to study participation or concurrent GSK medication/vaccine | | | | | | |
| Pregnancies | | | | | | |

V = visit; D = Day; AE = adverse event; SAE = serious adverse event.

### 8.3.2. Post-Study adverse events and serious adverse events

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 12. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study vaccines, the investigator will promptly notify the Study Contact for Reporting SAEs.

## 8.3.3. Evaluation of adverse events and serious adverse events

### 8.3.3.1. Active questioning to detect adverse events and serious adverse events

As a consistent method of collecting AEs, the subject or the subject's parent(s)/LAR(s) should be asked a non-leading question such as:

'*Have you felt different in any way since receiving the vaccine or since the previous visit?*' (for adult subjects)

OR

'*Has your child acted differently or felt different in any way since receiving the vaccine or since the last visit?*' (for pediatric subjects)

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE on the in the eCRF. The investigator is not allowed to send photocopies of the subject's medical records to GSK Biologicals instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

### 8.3.3.2. Assessment of adverse events

#### *8.3.3.2.1. Assessment of intensity*

The intensity of the following solicited AEs will be assessed as described:

**Table 13 Intensity scales for solicited AEs**

| Adverse Event | Intensity grade | Parameter |
|---|---|---|
| Fever* | | Record temperature in °C/°F |
| Induration at injection site | | Record greatest surface diameter in mm |
| Erythema at injection site | | Record greatest surface diameter in mm |
| Pain at injection site | Absent | None |
| | Mild | No interference with daily activity |
| | Moderate | Interferes with daily activity |
| | Severe | Prevents daily activity |
| Chills | Absent | Normal |
| | Mild | No interference with daily activity |
| | Moderate | Interferes with daily activity |
| | Severe | Prevents daily activity |
| Nausea | Absent | Normal |
| | Mild | No interference with daily activity |
| | Moderate | Interferes with daily activity |
| | Severe | Prevents daily activity |
| Myalgia | Absent | Normal |
| | Mild | No interference with daily activity |
| | Moderate | Interferes with daily activity |
| | Severe | Prevents daily activity |
| Arthralgia | Absent | Normal |
| | Mild | No interference with daily activity |
| | Moderate | Interferes with daily activity |
| | Severe | Prevents daily activity |
| Headache | Absent | Normal |
| | Mild | No interference with daily activity |
| | Moderate | Interferes with daily activity |
| | Severe | Prevents daily activity |
| Fatigue | Absent | Normal |
| | Mild | No interference with daily activity |
| | Moderate | Interferes with daily activity |
| | Severe | Prevents daily activity |
| Loss of appetite | Absent | Normal |
| | Mild | Eating less than usual with no effect on normal activity |
| | Moderate | Eating less than usual / interfered with normal activity |
| | Severe | Not eating at all |

* Fever is defined as temperature ≥ 38.0°C/100.4°C. preferred location for measuring temperature in this study will be the oral cavity.

The maximum intensity of local injection site erythema/induration will be scored at GSK Biologicals as follows:

Absent: < 25 mm diameter
Mild: ≥ 25 mm to ≤ 50 mm diameter
Moderate: > 50 mm to ≤ 100 mm diameter
Severe: > 100 mm diameter

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

- by 0.5 °C increments from 36.0°C up 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, 38.5, 39.0, 39.5, 40.0°C.

The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment will be based on the investigator's clinical judgement.

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.

The severity of unsolicited adverse events reported on the Adverse Events eCRF 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.

#### *8.3.3.2.2. Assessment of causality*

The investigator is obligated to assess the relationship between study vaccines and the occurrence of each AE/SAE using clinical judgement. In case of concomitant administration of multiple vaccines/products, if possible, the investigator should specify if the AE could be causally related to a specific vaccine/product administered (i.e investigational, control/placebo or co-administered vaccine). When causal relationship to a specific vaccine(s)/product(s) cannot be determined the investigator should indicate the AE to be related to all products.

Alternative plausible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study vaccines will be considered and investigated. The investigator will also consult the IB and/or SmPC and/or Prescribing Information for marketed products to determine his/her assessment.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the Expedited Adverse Events Report to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information and update the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

All solicited reactions will be considered causally related to vaccination. Causality of all other AEs should be assessed by the investigator using the following question:

*Is there a reasonable possibility that the AE may have been caused by the study vaccine?*

| | | |
|---|---|---|
| YES | : | There is a reasonable possibility that the study vaccine contributed to the AE. |
| NO | : | There is no reasonable possibility that the AE is causally related to the administration of the study vaccine. There are other, more likely causes and administration of the study vaccine is not suspected to have contributed to the AE. |

If an event meets the criteria to be determined as 'serious' (see Section 8.1.2), additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the vaccine, if applicable.
- Erroneous administration.
- Other cause (specify).

#### 8.3.3.3. Assessment of outcomes

The investigator will assess the outcome of all unsolicited AEs (including SAEs) recorded during the study as:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).

#### 8.3.3.4. Medically attended visits

For each solicited and unsolicited symptom the subject experiences, the subject/subject's parent(s)/LAR(s) will be asked if he/she /the subject received medical attention defined as hospitalization, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information will be recorded in the eCRF.

## 8.4. Reporting of serious adverse events, pregnancies, and other events

### 8.4.1. Prompt reporting of serious adverse events, pregnancies, and other events to GSK Biologicals

SAEs that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in Table 14, once the investigator determines that the event meets the protocol definition of a SAE.

Pregnancies that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in Table 14, once the investigator becomes aware of the pregnancy.

**Table 14 Timeframes for submitting serious adverse event, pregnancy and other events reports to GSK Biologicals**

| Type of Event | Initial Reports | | Follow-up of Relevant Information on a Previous Report | |
|---|---|---|---|---|
| | Timeframe | Documents | Timeframe | Documents |
| **SAEs** | 24 hours*‡ | electronic Expedited Adverse Events Report | 24 hours* | electronic Expedited Adverse Events Report |
| **Pregnancies** | 2 weeks* | electronic pregnancy report | 2 weeks* | electronic pregnancy report |

* Timeframe allowed after receipt or awareness of the information.
‡ The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.

### 8.4.2. Contact information for reporting serious adverse events and pregnancies

| Study Contact for Reporting SAEs and pregnancies |
|---|
| **Refer to the local study contact information document.** |
| **Back-up Study Contact for Reporting SAEs and pregnancies** |
| 24/24 hour and 7/7 day availability:<br><br>**GSK Biologicals Clinical Safety & Pharmacovigilance**<br><br>Outside US & Canada sites:<br>Fax: PPD or PPD<br>Email address: PPD<br><br>US sites only:<br>Fax: PPD<br><br>Canadian sites only:<br>Fax: PPD |

### 8.4.3. Completion and transmission of SAE reports to GSK Biologicals

Once an investigator becomes aware that a SAE has occurred in a study subject, the investigator (or designate) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS. The report will always be completed as thoroughly as possible with all available details of the event. Even if the investigator does not have all information regarding a SAE, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report. The investigator will be required to confirm the review of the SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.

#### 8.4.3.1. Back-up system in case the electronic reporting system does not work

If the electronic reporting system does not work, the investigator (or designate) must complete, then date and sign a paper Expedited Adverse Events Report and fax it to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within 24 hours.

This back-up system should only be used if the electronic reporting system is not working and NOT if the system is slow. As soon as the electronic reporting system is working again, the investigator (or designate) must complete the electronic Expedited Adverse Events Report within 24 hours. The final valid information for regulatory reporting will be the information reported through the electronic SAE reporting system.

### 8.4.4. Completion and transmission of pregnancy reports to GSK Biologicals

Once the investigator becomes aware that a subject is pregnant, the investigator (or designate) must complete the required information onto the electronic pregnancy report WITHIN 2 WEEKS.

Note: Conventionally, the estimated gestational age (EGA) of a pregnancy is dated from the first day of the last menstrual period (LMP) of the cycle in which a woman conceives. If the LMP is uncertain or unknown, dating of EGA and the estimated date of delivery (EDD) should be estimated by ultrasound examination and recorded in the pregnancy report.

### 8.4.5. Updating of SAE and pregnancy information after removal of write access to the subject's eCRF

When additional SAE or pregnancy information is received after removal of the write access to the subject's eCRF, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in Table 14.

### 8.4.6. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.4.1. GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

Investigator safety reports are prepared according to the current GSK policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to the study vaccines and unexpected. The purpose of the report is to fulfil specific regulatory and GCP requirements, regarding the product under investigation.

## 8.5. Follow-up of adverse events, serious adverse events, and pregnancies

### 8.5.1. Follow-up of adverse events and serious adverse events

#### 8.5.1.1. Follow-up during the study

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; refer to Table 14).

All SAEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the last visit of the subject.

All AEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until 30 days after the last vaccination.

#### 8.5.1.2. Follow-up after the subject is discharged from the study

The investigator will follow subjects:

- with SAEs, or subjects withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilized, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.

If the investigator receives additional relevant information on a previously reported SAE, he/she will provide this information to GSK Biologicals using a paper/ electronic Expedited Adverse Events Report and/or pregnancy report as applicable.

GSK Biologicals may request that the investigator performs or arranges the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognized follow-up period, GSK Biologicals will be provided with any available post-mortem findings, including histopathology.

### 8.5.2. Follow-up of pregnancies

Pregnant subjects will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK Biologicals using the electronic pregnancy report and the Expedited Adverse Events Report if applicable. Generally, the follow-up period doesn't need to be longer than six to eight weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs for this study, if the pregnancy outcome is a SAE, it should always be reported as SAE.

## 8.6. Treatment of adverse events

Treatment of any AE is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of a SAE should be recorded in Expedited Adverse Event Report of the subject's eCRF (refer to Section 6.7).

## 8.7. Unblinding

GSK Biologicals' policy (which incorporates ICH E2A guidance, EU Clinical Trial Directive and US Federal Regulations) is to unblind the report of any SAE which is unexpected and attributable/suspected to be attributable to the study vaccines, prior to regulatory reporting. The GSK Biologicals' Central Safety Physician is responsible for unblinding the treatment assignment in accordance with the specified timeframes for expedited reporting of SAEs (refer to Section 8.4.1).

## 8.8. Emergency unblinding

Unblinding of a subject's individual treatment code should occur only in the case of a medical emergency, or in the event of a serious medical condition, when knowledge of the treatment is essential for the clinical management or welfare of the subject, as judged by the investigator.

The emergency unblinding process consists of the automated system SBIR that allows the investigator to have unrestricted, immediate and direct access to the subject's individual study treatment.

The investigator has the option of contacting a GSK Biologicals' On-call Central Safety Physician (or Backup) if he/she needs medical advice or needs the support of GSK to perform the unblinding (i.e. he/she cannot access the automated Internet-based system).

Any emergency unblinding must be fully documented by using the Emergency Unblinding Documentation Form, which must be appropriately completed by the investigator and sent within 24 hours to GSK Biologicals.

| **GSK Biologicals' Contact information for Emergency Unblinding**<br><br>**24/24 hour and 7/7 day availability** |
|---|
| **GSK Biologicals' Central Safety Physician:**<br><br>Outside US/Canada:<br>PPD (GSK Biologicals Central Safety Physician on-call)<br><br>For US/Canada only:<br>PPD (GSK Biologicals Central Safety Physician on-call)<br><br>**GSK Biologicals' Central Safety Physician Back-up:**<br><br>Outside US/Canada:<br>PPD<br><br>US/Canada only:<br>PPD<br><br>**Emergency Unblinding Documentation Form transmission:**<br><br>Outside US & Canada:<br>Fax: PPD or PPD<br><br>US/Canada only:<br>Fax: PPD |

## 8.9. Subject card

Study subjects/subjects' parents/LARs must be provided with the address and telephone number of the main contact for information about the clinical study.

The investigator (or designate) must therefore provide a "subject card" to each subject/ subject's parent(s)/LAR(s). In an emergency situation this card serves to inform the responsible attending physician that the subject is in a clinical study and that relevant information may be obtained by contacting the investigator.

Subjects/subjects' parents/LARs must be instructed to keep subject cards in their possession at all times during the study duration.

# 9. SUBJECT COMPLETION AND WITHDRAWAL

## 9.1. Subject completion

A subject who is available for the concluding contact foreseen in the protocol is considered to have completed the study.

## 9.2. Subject withdrawal

Withdrawals will not be replaced.

### 9.2.1. Subject withdrawal from the study

From an analysis perspective, a 'withdrawal' from the study refers to any subject who was not available for the concluding contact foreseen in the protocol.

All data collected until the date of withdrawal/last contact of the subject will be used for the analysis.

A subject is considered a 'withdrawal' from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this subject from the date of withdrawal/last contact.

Investigators will make an attempt (3 telephone calls on different days and different times of day, and a certified letter to the last known address) to contact those subjects who do not return for scheduled visits or follow-up.

Information relative to the withdrawal will be documented in the eCRF. The investigator will document whether the decision to withdraw a subject from the study was made by the subject himself/herself, by the subject's parent(s)/LAR(s), or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Unsolicited non-serious adverse event.
- Solicited adverse event
- Protocol violation (specify).
- Consent withdrawal, not due to an adverse event*.
- Moved from the study area.
- Lost to follow-up.
- Other (specify).

  * In case a subject is withdrawn from the study because he/she/the subject's parent(s)/LAR(s) has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject/subject's parent(s)/LAR(s), in the eCRF.

Subjects who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn from the study as result of a SAE/AE until resolution of the event (see Section 8.5.1.2).

# 10. STATISTICAL METHODS

## 10.1. Primary endpoints

The following measures will be summarized:

- hSBA GMTs against *N. meningitidis* serogroup A at Day 29, for each vaccine group and between-group ratios (between vaccine groups ACWY_Liq24 and ACWY_1, and ACWY_Liq30 and ACWY_2).

## 10.2. Secondary endpoints

The following measures will be summarized:

- hSBA GMTs against *N. meningitidis* serogroups A (except Day 29), C, W and Y at Day 1 and at Day 29, for each vaccine group and between-group ratios (between vaccine serogroups ACWY_Liq24 and ACWY_1, and ACWY_Liq30 and ACWY_2).
- Within-group ratios of hSBA GMTs against *N. meningitidis* serogroups A, C, W and Y at Day 29 compared to Day 1, for each vaccine group.

- Percentages of subjects with a ≥ 4-fold rise in post-vaccination hSBA titer for *N. meningitidis* serogroups A, C, W and Y at Day 29 compared to Day 1, for each vaccine group and between-group differences (between vaccine groups ACWY_Liq24 and ACWY_1, and ACWY_Liq30 and ACWY_2).

  Note: A 4-fold rise is defined as: a) for individuals whose pre-vaccination titers are < the LOD, the post-vaccination titers must be ≥ 4-fold the LOD or ≥ the LLOQ whichever is greater; b) for individuals whose pre-vaccination titers are ≥ the LOD and ≤ the LLOQ, the post-vaccination titers must be at least four times the LLOQ; c) for individuals whose pre-vaccination titers are > the LLOQ, the post-vaccination titers must be at least four times the pre-vaccination titer.

- Percentages of subjects with hSBA titer ≥8 and ≥LLOQ* against *N. meningitidis* serogroups A, C, W and Y at Day 1 and at Day 29, for each vaccine group and between-group differences (between vaccine groups ACWY_Liq24 and ACWY_1, and ACWY_Liq30 and ACWY_2).

  * Note: To be assessed for each serogroup if the pre-defined LLOQ value for that serogroup is >8.

Safety of the study vaccine formulations will be evaluated for all vaccine groups in terms of the frequency (percentage) of reported adverse events including:

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

## 10.3. Determination of sample size

With an evaluable sample size of 375 subjects in each group being tested for non-inferiority, there will be approximately 90% power to reject the null hypothesis that the ratio of the hSBA GMT of the ACWY_Liq24 group (or ACWY_Liq30 group) to the ACWY_1 group (or ACWY_2 group) is equal to or less than 0.5 (given an underlying ratio of 0.8), assuming a common standard deviation (on log scale) of 0.861 (upper limit of the 80% confidence interval of the SD observed in study V59P13 for serogroup A in the age group 11–55 years), using a two group t-test with a 0.025 one-sided significance level. Overall power for both hypotheses will be approximately 81%. Assuming a 10% dropout rate, a total of approximately 1668 subjects will need to be enrolled in the study, with 417 subjects randomized to each of groups ACWY_1, ACWY_2, ACWY_Liq24 and ACWY_Liq30.

Calculations have been performed using "*Two-Sample T-Test Assuming Equal Variance (Enter Difference)"* procedure in PASS 2012 (Power Analysis and Sample Size Version 12.0.2).

## 10.4. Analysis Sets

### 10.4.1. 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.

### 10.4.2. All Exposed Set

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

### 10.4.3. Safety Set

#### 10.4.3.1. 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.

#### 10.4.3.2. Unsolicited Safety Set (unsolicited adverse events)

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

#### 10.4.3.3. 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).

### 10.4.4. Full Analysis Set (FAS) for immunogenicity

**FAS (Day 29)**

All subjects in the All Enrolled Set who:

- Are randomized;
- Receive the study vaccination;
- Provide an evaluable serum samples at Day 29 that has an available result for serogroup A (primary objective)/ for at least one serogroup (secondary objectives). For percentages of subjects with ≥ 4-fold rise, a baseline (Day 1) and a Day 29 result for at least one serogroup will be needed.

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).

### 10.4.5. Per Protocol (PP) Set for Immunogenicity

All subjects in the FAS (Day 29) who:

- Correctly receive the vaccine (i.e., receive the vaccine to which the subjects is randomized and at the scheduled time point).
- Have no protocol deviations leading to exclusion as defined prior to unblinding / analysis.
- Are not excluded due to other reasons defined prior to unblinding or analysis

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

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

- Subjects who withdrew informed consent.

### 10.4.6. Other Analysis Sets

There are no additional analysis sets.

### 10.4.7. Subgroups

A subgroup analysis for GMTs, percentage of subjects with hSBA titer ≥ 8 and ≥ LLOQ* against N. meningitidis serogroups A, C, W and Y at Day 29, will be performed for subjects who were seronegative at baseline.

In addition, subgroup analyses will be performed for GMTs, 4-fold rise, percentage of subjects with hSBA titer ≥ 8 and ≥ LLOQ* by sex, by race, by country, and by age group (≥ 10 to < 18 YoA and ≥ 18 to ≤ 40 YoA).

* Note: To be assessed for each serogroup if the pre-defined LLOQ value for that serogroup is > 8.

## 10.5. Derived and transformed data

- Immunogenicity
  - Assay cut-off and unit will be determined following validation of the MenACWY hSBAs. This will be documented in the clinical report.
  - A seronegative subject is a subject whose titer is below the LOD.
  - A seropositive subject is a subject whose titer is greater than or equal to the LOD.

- The Geometric Mean Titers (GMTs) calculations are performed by taking the anti-log of the mean of the log concentration/titer transformations. Values to be used for the antibody concentrations/titers below the assay cut-off will be described in the Statistical Analysis Plan (SAP).
- Handling of missing data: for a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced.

- Reactogenicity and Safety
  - Handling of missing data: Subjects will be analysed to the extent that they are 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 denominator for the time period in which they have no available safety data collected.

## 10.6. Analysis of demographics

Age, height and weight at enrollment 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.

## 10.7. Analysis of immunogenicity

The primary analysis will be based on the per-protocol set for analysis of immunogenicity. If, in any study group and timepoint, the percentage of vaccinated subjects with serological results excluded from the per-protocol set for analysis of immunogenicity is 5% or more, a second analysis based on the FAS will be performed to complement the per-protocol analysis.

**GMTs, between-group ratios of GMTs and within-group Geometric Mean Ratios (GMRs)**

The hSBA titers at each visit will be logarithmically transformed (base10) to obtain approximately normally distributed data. For each *N. meningitidis* serogroup A, C, W and Y, GMTs will be calculated, with their associated two-sided 95% CIs, by exponentiating the corresponding log-transformed means and their 95% CIs.

The between-group ratio of hSBA GMTs and corresponding 95% CI, at each of Day 1 and Day 29 against *N. meningitidis* serogroups A, C, W and Y will be obtained by exponentiating the mean between-group differences in log-transformed titers and the corresponding 95% CIs at each of the specified timepoints. Comparisons will be evaluated between vaccine groups ACWY_Liq24 and ACWY_1, and between vaccine groups ACWY_Liq30 and ACWY_2.

Within each study group and for each serogroup, GMRs will be calculated at Day 29 versus Day 1. The GMRs and 95% CIs will be constructed by exponentiating the mean within-group differences in log-transformed titers and the corresponding 95% CIs.

The mean differences will be obtained from an Analysis of Covariance (ANCOVA) including pre-vaccination titer (Day 1) as a covariate and with vaccine group and center (if applicable) as factors in the model.

**Percentage of subjects with a ≥ 4-fold rise in post-vaccination hSBA titer (Day 29)**

The percentage of subjects with a ≥ 4-fold rise in post-vaccination hSBA titer (at Day 29 compared to Day 1) and associated two-sided 95% Clopper- Pearson CIs will be computed by group and *N. meningitidis* serogroups A, C, W and Y. Differences in percentages and associated 95% CIs between study groups will be calculated using the Miettinen and Nurminen score method. Comparisons will be evaluated between vaccine groups ACWY_Liq24 and ACWY_1, and between vaccine groups ACWY_Liq30 and ACWY_2.

**Percentage of subjects with hSBA titer ≥ 8 and ≥LLOQ* (Day 1 and Day 29)**

For each study group the percentage of subjects with hSBA titer ≥8 and ≥LLOQ* and associated two-sided 95% Clopper-Pearson CIs will be computed by the *N. meningitidis* serogroups A, C, W and Y on Day 1 and Day 29. Differences in percentages and associated 95% CIs between study groups will be calculated using the Miettinen and Nurminen score method. Comparisons will be evaluated between vaccine groups ACWY_Liq24 and ACWY_1, and between vaccine groups ACWY_Liq30 and ACWY_2.

* Note: To be assessed for each serogroup if the pre-defined LLOQ value for that serogroup is >8.

## 10.8. Analysis of safety

Safety analysis will be performed on the solicited safety set for solicited reactions and on unsolicited safety set for unsolicited adverse events.

### 10.8.1. 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: Absent (0-24 mm), Mild (25-50 mm), Moderate (51-100 mm) or 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 summarized according to “mild”, “moderate” or “severe”.

Each solicited local and systemic adverse event will also be further summarized as “absent” 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 temperature will be summarized separately according to the 3 schemes described below and will be broken down according to route of measurement:

- by 0.5 °C increments from 36.0°C up 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, 38.5, 39.0, 39.5, 40.0°C.

### 10.8.2. Analysis of Unsolicited Adverse Events

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

## 10.9. Interpretation of analyses

### 10.9.1. Primary immunogenicity objective

The analysis population for the non-inferiority analysis is the Per Protocol Set (PPS).

To demonstrate non-inferiority of the investigational MenACWY liquid vaccines to the currently licensed MenACWY vaccine (*Menveo*), the lower limit of the two-sided 95% confidence interval (CI) for the hSBA GMT ratios for serogroup A at Day 29, must be greater than 0.5. Hierarchical hypothesis testing will be performed at overall Type I Error of 2.5% (one-sided) using non-inferiority margin of 0.5 for GMT ratios.

The two hypotheses will be tested sequentially as follows:

1. Group ACWY_Liq24 versus Group ACWY_1

Null hypothesis (inferiority): $\mu_{ACWY\_Liq24} - \mu_{ACWY\_1} \leq \log_{10}(0.5)$ *versus*

Alternative hypothesis (non-inferiority): $\mu_{ACWY\_Liq24} - \mu_{ACWY\_1} > \log_{10}(0.5)$

Where: 0.5 is the non-inferiority margin for the ratio of GMTs between Group ACWY_Liq24 and Group ACWY_1; $\mu_{ACWY\_Liq2}$ and $\mu_{ACWY\_}$ are the population means of the logarithmically (base of 10) transformed titers for serogroup A in Group ACWY_Liq24 and Group ACWY_1, respectively.

If the lower limit of the two-sided 95% CI for the hSBA GMT ratio is greater than 0.5, then we conclude non-inferiority and proceed to test the next hypothesis for Group ACWY_Liq30 versus Group ACWY_2. Otherwise, further hypothesis testing is not conducted.

2. Group ACWY_Liq30 versus Group ACWY_2

Null hypothesis (inferiority): $\mu_{ACWY\_Liq30} - \mu_{ACWY\_2} \leq \log_{10}(0.5)$ *versus*

Alternative hypothesis (non-inferiority): $\mu_{ACWY\_Liq30} - \mu_{ACWY\_2} > \log_{10}(0.5)$

If the lower limit of the two-sided 95% CI for the hSBA GMT ratio is greater than 0.5, then we conclude non-inferiority.

### 10.9.2. Secondary Immunogenicity Objectives

Analysis of secondary objectives will be descriptive.

## 10.10. Conduct of analyses

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

### 10.10.1. Sequence of analyses

The analysis will be performed in the following steps:

- An interim analysis will be performed after availability of the Visit 2 (day 29) immunogenicity and safety data for both the MenACWY liquid aged for approximately 24 months (ACWY_Liq24) and the *Menveo* arm 1 (ACWY_1). This interim analysis might be reported in an interim clinical study report (CSR) for regulatory purposes.
- The analyses of safety data for the ACWY_Liq24 and ACWY_1 arms received after Visit 2 (Day 29) until study end (Day 181) will be performed after study end, once all data are available, together with the analysis performed on the immunogenicity and safety data for both the MenACWY liquid aged for approximately 30 months (ACWY_Liq30) and the *Menveo* arm 2 (ACWY_2). A final integrated CSR including the interim and the final analyses will be written at this point in time.

An integrated clinical study report containing all data will be written and made available to the investigators.

### 10.10.2. Statistical considerations for interim analyses

The interim and final analyses will be performed sequentially. An interim analysis will include the analyses of the primary endpoint and secondary endpoints and safety data. The analysis will be performed after the availability of the Visit 2 immunogenicity and safety data for the MenACWY liquid aged for approximately 24 months (ACWY_Liq24) and ACWY_1.

The interim analysis will be performed by the BioStatistics and Statistical Programming department. Details on how the interim analysis will be performed will be added to the Statistical Analysis Plan.

# 11. ADMINISTRATIVE MATTERS

To comply with ICH GCP administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality, public disclosure requirements and publications must be fulfilled.

## 11.1. Electronic Case Report Form instructions

A validated GSK defined electronic data collection tool will be used as the method for data collection.

In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

The investigator will be provided with an electronic format in read only mode of the final version of the data generated at the investigational site once the database is archived and the study report is complete and approved by all parties.

## 11.2. Subject Diary

Electronic Diaries (eDiaries), 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 of data recorded by the subjects/parents/LARs will be allowed once diary completion for that day has been performed.
- The Subject Diary will be designed in such a way as to prevent any blank, incomplete or biologically implausible entries. Subjects/parents/LARs will be instructed to fully complete the Subject Diary each day, as per the instructions provided.
- At or just in advance of each subject visit, site staff must review the Subject Diary data via the provider's web portal. It is necessary for site staff to acknowledge in the source documents that review of Subject Diary data for the preceding post-vaccination period has been performed. At the end of the study it is necessary for the investigator to acknowledge in the eCRF that the review of Subject Diary data has been performed for each subject.
- For vaccination visits, site staff must ensure that each subject's Diary is prepared for data capture in the ensuing post-vaccination period by confirming the visit within the eDiary/eDiary system.
- Any new safety information reported during the site visit (including a solicited adverse event) cannot be entered into the Subject Diary. Such information must be described in the source notes as a verbally-reported event. Any adverse event reported in this fashion must be described as an unsolicited adverse event and therefore entered on the adverse event page of the eCRF.

## 11.3. Study Monitoring by GSK Biologicals

GSK will monitor the study to verify that, amongst other items, the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol, any other study agreements, GCP and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform a eCRF review and a Source Document Verification (SDV). By SDV we understand verifying eCRF entries by comparing them with the source data that will be made available by the investigator for this purpose.

The Source Documentation Agreement Form describes the source data for the different data in the eCRF. This document should be completed and signed by the site monitor and investigator and should be filed in the investigator's study file. Any data item for which the eCRF will serve as the source must be identified, agreed and documented in the source documentation agreement form.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

## 11.4. 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 must 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); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a 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 reproductions.

GSK will inform the investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum 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/institution must 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 leaves the site.

## 11.5. Quality assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

## 11.6. Posting of information on publicly available clinical trial registers and publication policy

GSK assures that the key design elements of this protocol will be posted on the GSK website and in publicly accessible database(s) such as clinicaltrials.gov, in compliance with the current regulations.

GSK also assures that results of this study will be posted on the GSK website and in publicly accessible regulatory registry(ies) within the required time-frame, in compliance with the current regulations. The minimal requirement is to have primary endpoint summary results disclosed at latest 12 months post primary completion date (PCD) and to have secondary endpoint disclosed at latest 12 months after the last subject last visit (LSLV) as described in the protocol.

As per EU regulation, summaries of the results of GSK interventional studies (phase I-IV) in paediatric/adult population conducted in at least one EU member state will be posted on publicly available EMA registers within 6 months of EoS (as defined in the protocol) in the concerned EU member state. However, where, for scientific reasons detailed in the protocol, it is not possible to submit a summary of the results within 6 months in the concerned EU member state, the summary of results shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with a justification.

GSK also aims to publish the results of these studies in searchable, peer reviewed scientific literature and follows the guidance from the International Committee of Medical Journal Editors.

## 11.7. Provision of study results to investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK Biologicals will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

## 11.8. Data Sharing

Under the framework of the SHARE initiative, results of GSK studies may be combined with non- GSK studies, to investigate further about the study product(s) and other product(s), and /or the disease/condition under investigation and related diseases and conditions.

# 12. COUNTRY SPECIFIC REQUIREMENTS

## 12.1. Requirements for France

This section includes all the requirements of the French law (n° 2004-806 of 9th August 2004), and identifies, item per item, the mandatory modifications or additional information to the study protocol and includes specifics GSK requirements.

1. **Concerning the «STUDY POPULATION»**

- In line with the local regulatory requirements, the following text in section «OTHER STUDY ELIGIBILITY CRITERIA CONSIDERATIONS» is added:

  A subject will be eligible for inclusion in this study if he/she is either affiliated to or beneficiary of a social security category.

  It is the investigator's responsibility to ensure and to document (in source document - patient notes) that the patient is either affiliated to or beneficiary of a social security category.

2. **Concerning the "DATA ANALYSIS AND STATISTICAL CONSIDERATIONS" and specially in the "SAMPLE SIZE ASSUMPTION"**

The expected number of patients to be recruited in France is declared to the French regulatory authority.

3. **Concerning the "STUDY CONDUCT CONSIDERATIONS"**

- In section "REGULATORY AND ETHICAL CONSIDERATIONS, INCLUDING THE INFORMED CONSENT PROCESS"

  Concerning **the process for informing the patient** or his/her legally authorized representative, the following text is added:

– French Patient Informed Consent form is a document which summarizes the main features of the study and allows collection of the patient's written consent in triplicate. It also contains a reference to the authorisation of ANSM and the approval from the French Ethic committee and the maintenance of confidentiality of the returned consent form by GSK France.

Concerning **the process for obtaining** subject informed consent, **if the patient is under 18 years old,** the following text is added:

– The informed consent of the holders of parental authority must be obtained before the beginning of the study. The consent of the child will be also sought when he/she is old enough to express his/her opinion. His/her refusal or the revocation of his/her consent cannot be disregarded. If there is only one holder of parental authority, the investigator will ask the present person to file, date and sign the affidavit (in triplicate) indicating his situation regarding the parental authority. A copy of this affidavit is joined to each consent form.

– If these directives are not followed, the patient inclusion could be considered as a protocol violation and the data of this case won't be taken into account.

Concerning the management of the Patient Informed Consent forms, the following text is added:

– The first copy of the Patient Informed Consent form is kept by the investigator. The second copy is kept by the Medical Direction of GSK France and the last copy is given to the patient or his/her legally authorized representative.

– The second copy of all the consent forms will be collected by the investigator under the Clinical Research Assistant’s (CRAs) control, and placed in a sealed envelope bearing only:

– the study number,

– the identification of the Centre: name of the principal investigator and centre number,

– the number of informed consents,

– the date,

– and the principal investigator’s signature.

Then, the CRA hands the sealed envelope over to the Medical Direction, for confidential recording, under the responsibility of the Medical Director.

- In section concerning the “NOTIFICATION TO THE HOSPITAL DIRECTOR” the following text is added:

  In accordance with Article L1123-13 of the Public Health Code, the Hospital Director is informed of the commitment to the trial in his establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial (R.1123-63).

- In section concerning the "INFORMATION TO THE HOSPITAL PHARMACIST" the following text is added:

  In accordance with Article R.1123-64 of the Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in his establishment. The Pharmacist is supplied with a copy of the protocol (which allows him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g. included in the CIB), the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial.

- In section "DATA MANAGEMENT" the following text is added:

  Within the framework of this clinical trial, data regarding the identity of the investigators and/or co-investigators and/or the pharmacist if applicable, involved in this clinical trial, and data regarding the patients recruited in this clinical trial (patient number, treatment number, patient status with respect to the clinical trial, dates of visit, medical data) will be collected and computerized in GSK data bases by GSK Laboratory or on its behalf, for reasons of follow up, clinical trial management and using the results of said clinical trial. According to the Act n° 78-17 of 6th January 1978 further modified, each of these people aforesaid has a right of access, correction and opposition on their own data through GSK Laboratory (Clinical Operations Department).

- In the section concerning "DEMOGRAPHIC DATA", the following text is added:

  In accordance with the data processing and freedom French law dated on 6th of January 1978 modified on the 6th of August 2004 - article 8, the ethnic origin can only be collected if the collection of this data is justified within the framework of this study.

- In the section concerning "TESTING OF BIOLOGICAL SAMPLES" the following text is added:

  In accordance with the Article L1211-2 of the French Public Health Code, a biological sample without identified purpose at the time of the sample and subject's preliminary information is not authorized.

4. **Concerning the «SAE»**

- In section "TRANSMISSION OF THE SAE REPORTS":

  In case of paper CRF, the SAE Reports have to be transmitted to the GSK France Drug Safety Department, which name, address and phone number are:

  Département de Pharmacovigilance

  Laboratoire GlaxoSmithKline

  23 rue PPD

  92500 RUEIL MALMAISON

  Tel : PPD

  Fax : PPD

  PPD

5. **Monitoring visits**

The Health Institution and the Investigator agree to receive on a regular basis a Clinical Research Assistant (CRA) of GSK or of a service provider designated by GSK. The Health Institution and the Investigator agree to be available for any phone call and to systematically answer to all correspondence regarding the Study from GSK or from a service provider designated by GSK. In addition, the Health Institution and the Investigator agree that the CRA or the service provider designated by GSK have direct access to all the data concerning the Study (test results, medical record, etc. …). This consultation of the information by GSK is required to validate the data registered in the electronic Case Report Form (eCRF), in particular by comparing them directly to the source data. In accordance with the legal and regulatory requirements, the strictest confidentiality will be respected.

6. **Data entry into the eCRF**

The Health Institution and the Investigator agree to meet deadlines, terms and conditions of the Study's eCRF use here below:

The Health Institution and the Investigator undertake:

i. That the Investigator and the staff of the investigator center make themselves available to attend the training concerning the computer system dedicated to the eCRF of the Study provided by GSK or by a company designated by GSK.

ii. That the Investigator and the staff of the investigator center use the IT Equipment loaned and/or the access codes only for the purpose of which they are intended and for which they have been entrusted to them, namely for the Study achievement, to the exclusion of any other use.

iii. That the Investigator and the staff of the investigator center use the IT Equipment loaned according to the specifications and manufacturer's recommendations which will have been provided by GSK.

iv. To keep the IT Equipment and/or access codes in a safe and secure place and to only authorize the use of this IT Equipment by investigator center staff designated by the principal investigator to enter the data of the Study.

v. That the Investigator and the staff of the investigator center enter the data of the eCRF related to a patient visit in the 3 days following the date of the patient visit or, for the patient test results, in the 3 days following the reception of the results of such tests.

vi. That the Investigator resolves and returns to GSK the data queries issued by GSK or a service provider designated by GSK within 7 days after the reception of the request of clarification or in a period of one (1) day during the final stage of clarification of the data base or in such other period as provided by GSK and/or a company designated by GSK.

vii. To be responsible for the installation and payment of the required Internet connections needed for the use of the IT Equipment, Computer systems and/or access codes.

viii. To return at the end of the Study the IT Equipment and/or access codes to GSK or to any company designated by GSK and any training material and documentation. The IT Equipment cannot under any circumstances be kept by the Health Institution or the Investigator for any reason whatsoever.

7. **CTR publication**

It is expressly specified that GSK and/or the Sponsor can make available to the public the results of the Study by the posting of the said results on a website of the GSK GROUP named Clinical Trial Register (CTR) including the registration of all the clinical trials conduct by the GSK Group and this before or after the publication of such results by any other process.

8. **Data Protection French Law of 6 January 1978 (CNIL)**

In accordance with the Data Protection French Law of 6 January 1978 as modified, computer files used by GSK to monitor and follow the implementation and the progress of the Study are declared with the CNIL by GSK. The Investigator has regarding the processing data related to him a right of access, of rectification and of opposition with GSK in accordance with the legal provisions. This information can be transferred or be accessed to other entities of GSK Group in France, Britain or United States, what the Investigator agrees by the signature of the present Protocol.

# 13. REFERENCES

Centers for Disease Control and Prevention Metropolitan Atlanta Congenital Defects Program (CDC MACDP) guidelines. Birth defects and genetic diseases branch 6-digit code for reportable congenital anomalies; http://www.cdc.gov/ncbddd/birthdefects/documents/MACDPcode0807.pdf

EMA Guideline on the exposure to medicinal products during pregnancy: need for post-authorization data (Doc. Ref. EMEA/CHMP/313666/2005 ) 'adopted at Community level in May 2006); *http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011303.pdf*

Granoff DM, Feavers IM, Borrow R. Chapter 34. Meningococcal vaccines. In: Plotkin S, Orenstein WA, editors. Vaccines, 4th ed.: W. B. Saunders; 2003 (in press).

Haralambieva IA, Ovsyannikova IG, Kennedy RB, *et al*. Race and Sex-Based Differences in Cytokine Immune Responses to Smallpox Vaccine in Healthy Individuals. *Hum Immunol*. 2013; 74(10): 1263–1266.

Kollmann TR. Variation between Populations in the Innate Immune Response to Vaccine Adjuvants. *Front Immunol.* 2013; 4: 81.

Pérez-Losada M, Posada D, Arenas M, *et al*. Ethnic differences in the adaptation rate of HIV gp120 from a vaccine trial. *Retrovirology*. 2009; 6: 67.

Pollard AJ, Perrett KP, Beverley PC. Maintaining protection against invasive bacteria with protein–polysaccharide conjugate vaccines. *Nat Rev Immunol*. 2009; 9, 213-220.

Rosenstein NE, Fischer M, Tappero JW. Meningococcal vaccines. *Infect Dis Clin North Am* 2001; 15(1): 155-69.

# APPENDIX A LABORATORY ASSAYS

The following tests will be performed using the aliquots of serum:

- The induction of functional anti-meningococcal activity by bactericidal antibodies directed against *N. meningitidis* serogroups A, C, W and Y will be determined by a Serum Bactericidal Assay using human complement (hSBA) as exogenous complement source.
- The testing will be performed at the GSK Biologicals' laboratories or a laboratory designated by GSK Biologicals. Upon validation of the hSBA format, assay cut-offs and unit for each of the MenACWY serogroups will be determined and will be documented in the clinical report. Titres will be expressed as the reciprocal of the dilution resulting in 50% inhibition.

# APPENDIX B CLINICAL LABORATORIES

## Table 15 GSK Biologicals' laboratories

| Laboratory | Address |
|---|---|
| GSK Biological's Clinical Laboratory Sciences, Rixensart | Biospecimen Reception - B7/44<br>Rue de l'Institut, 89 - B-1330 Rixensart – Belgium |
| GSK Biological's Clinical Laboratory Sciences, Wavre-Nord Noir Epine | Avenue Fleming, 20 - B-1300 Wavre - Belgium |
| GSK Vaccines GmbH<br>Clinical Laboratory Sciences, Marburg, Germany | Emil-von-Behring-Str. 76<br>35041 Marburg<br>Germany |

# APPENDIX C AMENDMENTS TO THE PROTOCOL

| GlaxoSmithKline Biologicals SA<br><br>Vaccines R&D<br>Protocol Amendment 1 | |
|---|---|
| **eTrack study number and Abbreviated Title** | 207467 (MENACWY CONJ-069 [V59_78]) |
| **IND number** | 11278. |
| **EudraCT number** | 2017-003456-23 |
| **Amendment number:** | Amendment 1 |
| **Amendment date:** | 17 January 2018 |
| **Co-ordinating author:** | PPD (Lead Scientific Writer) |
| **Rationale/background for changes:**<br>• Two of the exclusion criteria were very similar and have therefore been combined into one exclusion criterion.<br>• The product specifications related to the *Corynebacterium diphtheriae* Cross Reacting Material 197 (CRM197) content of the investigational MenACWY liquid vaccine formulation have been updated.<br>• Clarification of the immunogenicity endpoints that will be included in the subgroups analysis.<br>• A change in the study personnel has been included on the protocol cover page.<br>• Some editorial changes have been made throughout the document, including a simplification of the names of the study vaccines. | |

**Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:**

Throughout the document the names of the study vaccines have been simplified, as follows:

- MenACWY~~-CRM~~
- ~~liquid~~ MenACWY~~-CRM~~ ***liquid***

On **the protocol cover page**, the following change has been made:

| | |
|---|---|
| **Co-ordinating author** | • PPD ***(Lead Scientific Writer)*** |

In **Section 4.3 Exclusion criteria for enrollment**, the following changes have been made:

3. Any ***(clinical)*** condition that in the judgment of the investigator would make intramuscular injection unsafe ***and/or represents a contraindication to intramuscular vaccination and blood draws***.
7. ~~Clinical conditions representing a contraindication to intramuscular vaccination and blood draws.~~

In **Section 6.1 Description of study vaccines**, the following changes have been made:

**Table 10 Study vaccines**

| Treatment name | Vaccine/product name | Formulation | Presentation | Volume to be administered | Number of doses |
|---|---|---|---|---|---|
| MenACWY liquid | ~~Menveo~~***MenACWY*** liquid | MenA=10µg CRM197; MenC=5µg CRM197; MenW=5µg CRM197; MenY=5µg CRM197; CRM197=***25.4-65.8***~~32.7-64.1~~µg | Liquid in a monodose vial | 0.5 ML | 1 |
| Licensed MenACWY *(Menveo*)* | MenA lyo | MenA=10µg CRM197; CRM197=16.7-33.3µg | Lyophilized component in a vial | 0.5 ML | 1 |
| | MenCWY liquid | MenC=5µg CRM197; MenW=5µg CRM197; MenY=5µg CRM197; CRM197=16-30.8µg | Liquid component in a vial | | |

* *Menveo* commercial formulation consisting of a MenA lyphophilized component and of a MenCWY liquid component to be reconstituted together before administration (0.5 mL)

In **Section 10.4.7 Subgroups**, the following changes have been made:

A subgroup analysis for GMTs***, percentages of subjects with hSBA titer ≥ 8 and ≥ LLOQ* against N. meningitidis serogroups A, C, W and Y at Day 29,*** will be performed for subjects who were seronegative at baseline. In addition, subgroup analyses will be performed for GMTs***,*** ~~and four~~***4***-fold rise***, percentages of subjects with hSBA titer ≥ 8 and ≥ LLOQ*** by sex, by race, by country, and by age group (≥ 10 to < 18 YoA and ≥ 18 to ≤ 40 YoA).

****Note: To be assessed for each serogroup if the pre-defined LLOQ value for that serogroup is > 8.***

| **GlaxoSmithKline Biologicals SA**<br><br>Vaccines R &D<br>**Protocol Amendment 2** | |
|---|---|
| **eTrack study number and Abbreviated Title** | 207467 (MENACWY CONJ-069 [V59_78]) |
| **IND number** | 11278 |
| **EudraCT number** | 2017-003456-23 |
| **Amendment number:** | Amendment 2 |
| **Amendment date:** | 15 March 2018 |
| **Co-ordinating author:** | PPD (Expert Scientific Writer) |

**Rationale/background for changes:**

- Table 1.3.1 has been updated to reflect the potential and identified risks for MenACWY vaccine in alignment with the current version of the EU-RMP.
- Table 13 "Intensity scales for solicited AEs" has been updated to correct the intensity scores of some of the AEs solicited.
- The text below Table 13 has been updated to change "redness/swelling" to "erythema/induration", in line with the local AEs solicited.

**Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:**

On **the protocol cover page**, the second coordinating author's name was deleted and only original protocol author's name was retained as per the template guidance.

In **Section 1.3, Benefit: Risk Assessment**, the risk table was updated to reflect the current potential and identified risks for MenACWY vaccine in alignment with the current version of the EU-RMP and as follows:

| Important Potential/Identified Risk | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| *Menveo* and investigational MenACWY liquid vaccine | | |
| ~~• Guillain-Barré syndrome~~<br>~~• Acute disseminated encephalomyelitis~~<br>~~• Thrombocytopenia~~<br>~~• Vasculitis including Kawasaki disease~~<br>~~• Brachial neuritis~~<br>~~• Facial Paresis~~<br>~~• Severe injection site reactions~~<br>~~• Systemic reactions (severe), including febrile convulsion~~<br>~~Vaccination failure (lack of efficacy)~~ | ~~Potential risks as included in the *Menveo* EU Risk Management Plan.~~ | ~~Accept as *Menveo* is a licensed product and the incidence of the potential risks is low to very low.~~ |

| Important Potential/Identified Risk | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| ***Important Identified risk: Reconstitution errors*** | ***Cases describing medication errors due to administration of the MenCWY conjugate liquid component only without reconstitution with the MenA conjugate lyophilized component, or due to administration of the MenA conjugate lyophilized component only after reconstitution with a different solvent, have been reported during the MenACWY clinical development program.*** | ***In several sections of the protocol (e.g. Section 6.1 "Description of study vaccines") it is clarified that the 2 vaccine components have to be reconstituted before vaccine injection.*** |
| ***Important potential risk: Guillain-Barré syndrome (GBS)*** | ***GBS has been observed with other vaccines. No cases have been reported during the MenACWY clinical development program.*** | ***GBS will be monitored through SAE collection.*** |
| ***Important potential risk: Acute disseminated encephalomyelitis (ADEM)*** | ***ADEM has been observed with other vaccines. Two cases from clinical trials were retrieved from the GSK's global safety database for MenACWY. None of them has provided sufficient evidence of a causal association between ADEM and MenACWY.*** | ***ADEM will be monitored through SAE collection.*** |
| ***Important potential risk: Thrombocytopenia*** | ***Immune thrombocytopenic purpura has been reported in association with several licensed vaccines. Two cases related to MenACWY were reported during the clinical development program, but none of them has provided a clear association between thrombocytopenia and the vaccine.*** | ***Immune thrombocytopenic purpura will be monitored through SAE collection.*** |
| ***Important potential risk: Facial paresis*** | ***Facial paresis was recognized as an important potential risk following the results of a sponsored observational study (V59_34OB) which found an imbalance of cases of facial paresis following vaccination with MenACWY, mainly when administered concomitantly with other vaccines. No cases of facial paresis were reported from interventional clinical trials.*** | ***Paralysis of the face is mentioned in the list of side effects in the ICF. Facial paresis will be monitored through SAE collection.*** |

| Important Potential/Identified Risk | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| ***Important potential risk: Vasculitis including Kawasaki disease (KD)*** | ***There were 7 cases of suspected KD reported in three clinical studies of Menveo. The occurrence of the cases in Menveo studies is consistent with the known epidemiology of KD in terms of geographic and temporal clustering, and seasonal variation. Therefore there is no evidence of a causal association between KD and MenACWY vaccine. As the exposure in clinical trial of subject was limited considering the incidence of the disease, KD is considered as a potential risk.*** | ***Vasculitis including Kawasaki disease will be monitored through SAE collection.*** |
| Study Procedures | | |
| Risk of blood sampling | Blood sampling associated risk of syncope, dizziness, infection at the site after or during venepuncture. | Blood samples will be obtained by a trained professional and medical assistance will be available.<br>The potential risk of feeling faint, or experiencing mild local pain, bruising, irritation or redness at the site where blood was taken, is mentioned in the ***Informed Consent Form (***ICF***)***. The amount of blood to be taken for sampling will not be harmful to the subject's health. |

For consistency throughout the protocol, the phrase "solicited symptoms" was changed to "solicited adverse events".

**Section 8.3.3.2.1, Assessment of intensity**, has been updated to correct the intensity scores of some of the AEs solicited and as follows.

## Table 13 Intensity scales for solicited AEs (Amended 15 March 2018)

| Adverse Event | Intensity grade | Parameter |
|---|---|---|
| Fever* | | Record temperature in °C/°F |
| Induration at injection site | | Record greatest surface diameter in mm |
| Erythema at injection site | | Record greatest surface diameter in mm |
| Pain at injection site | Absent | None |
| | Mild | ~~Any pain neither interfering with nor preventing normal every day activities.~~ ***No interference with daily activity*** |
| | Moderate | ~~Painful when limb is moved and interferes with every day activities.~~ ***Interferes with daily activity*** |
| | Severe | ~~Significant pain at rest. Prevents normal every day activities.~~ ***Prevents daily activity*** |
| Chills | Absent | Normal |
| | Mild | No interference with ***daily*** activity |
| | Moderate | Interferes with daily activity |
| | Severe | Prevents daily activity |
| Nausea | Absent | Normal |
| | Mild | No interference with ***daily*** activity |
| | Moderate | Interferes with daily activity |
| | Severe | Prevents daily activity |
| Myalgia | Absent | Normal |
| | Mild | No interference with ***daily*** activity |
| | Moderate | Interferes with daily activity |
| | Severe | Prevents daily activity |
| Arthralgia | Absent | Normal |
| | Mild | No interference with ***daily*** activity |
| | Moderate | Interferes with daily activity |
| | Severe | Prevents daily activity |
| Headache | Absent | Normal |
| | Mild | ~~Headache that is easily tolerated.~~ ***No interference with daily activity*** |
| | Moderate | ~~Headache that interferes with normal activity.~~ ***Interferes with daily activity*** |
| | Severe | ~~Headache that prevents normal activity.~~ ***Prevents daily activity*** |
| Fatigue | Absent | Normal |
| | Mild | ~~Fatigue that is easily tolerated.~~ ***No interference with daily activity*** |
| | Moderate | ~~Fatigue that interferes with normal activity.~~ ***Interferes with daily activity*** |
| | Severe | ~~Fatigue that prevents normal activity.~~ ***Prevents daily activity*** |
| Loss of appetite | Absent | Normal |
| | Mild | Eating less than usual with no effect on normal activity |
| | Moderate | Eating less than usual / interfered with normal activity |
| | Severe | Not eating at all |

* Fever is defined as temperature ≥ 38.0°C/100.4°F. preferred location for measuring temperature in this study will be the oral cavity.

The maximum intensity of local injection site ~~redness~~ ***erythema/induration*** ~~swelling~~ will be scored at GSK Biologicals as follows:

Absent: < 25 mm diameter
Mild: ≥ 25 mm to ≤ 50 mm diameter
Moderate: > 50 mm to ≤ 100 mm diameter
Severe: > 100 mm diameter

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

- by 0.5 °C increments from 36.0°C up 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, 38.5, 39.0, 39.5, 40.0°C.

The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment will be based on the investigator's clinical judgement.

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.

The severity of ***unsolicited adverse*** events reported on the Adverse Events eCRF 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.

# GlaxoSmithKline Biologicals SA

## Vaccines R&D
## Protocol Amendment 3

| | |
|---|---|
| **eTrack study number and Abbreviated Title** | 207467 (MENACWY CONJ-069 [V59_78]) |
| **IND number** | 11278. |
| **EudraCT number** | 2017-003456-23 |
| **Amendment number:** | Amendment 3 |
| **Amendment date:** | 08 February 2019 |
| **Co-ordinating author:** | PPD (Scientific Writer) |

**Rationale/background for changes:**

- An update in the list of contributing authors has been included on the protocol cover page.
- Wording of *Section 5.3 Method of blinding* and *Section 5.7.3 Laboratory assays* has been updated to align with the current Company Standards related to blinding for sample testing.

**Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:**

On **the protocol cover page**, the contributing authors list has been updated, without deleting previous authors as per template guidance.

**Contributing authors (continued)**

- PPD (Director Clinical Statistics)
- PPD ***(Lead Statistician)***
- PPD (Study Statistician)
- PPD (Study Statistician~~; Rosemind Consulting for GSK biologicals~~)
- PPD, PPD ***and*** PPD (Study Delivery Lead)
- PPD (Clinical Trial Supply Manager)
- PPD (Clinical Laboratory Sciences [CLS] Read-out Team Leader)
- PPD (Clinical Safety representative)
- PPD and PPD (CLS Study Managers)

- PPD (Oversight Data Manager)
- PPD and PPD (Study Data Managers)
- PPD ***(Lead Scientific Writer)***
- PPD ***(Scientific Writer)***
- PPD (Regulatory Affairs representative)
- PPD (Global Patents representative)
- PPD (Clinical and Epidemiology Research & Development Project Lead)

In **Section 5.3 Methods of blinding**, the following changes have been made:

The laboratory in charge of the laboratory testing will be blinded to the treatment ***as well as to the*** ~~,~~ subject ~~and visit~~ number~~, and codes will be used to link the subject, visit and study (without any link to the treatment attributed to the subject) to each sample~~. ***In addition, a randomly selected subject code will be used for each timepoint tested. This subject coding will prevent the laboratory from linking the consecutive visits to a specific subject***.

In **Section 5.7.3 Laboratory assays**, the following changes have been made:

The measure of immunogenicity used in this study is standard, i.e., widely used and generally recognized as reliable, accurate, and relevant (able to describe the quality and extent of the immune response). Testing will be conducted by a GSK or designated laboratory in a blinded manner towards the subject number ***and*** ~~,~~ the treatment arm ***(please refer to Section 5.3 Method of blinding).*** ~~and to the visit~~.