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

| | |
|---|---|
| **Primary study vaccine and number** | • GlaxoSmithKline (GSK) Biologicals' meningococcal MenABCWY vaccine (GSK3536819A) |
| **Other study vaccines** | • GSK Biologicals' meningococcal rMenB+OMV NZ vaccine (*Bexsero*; GSK3536829A)<br>• GSK Biologicals' meningococcal MenACWY vaccine (*Menveo*; GSK3536820A) |
| **eTrack study number and abbreviated title** | 208205 MENABCWY-016 (V102_19) |
| **EudraCT number** | 2017-005128-12 |
| **Date of protocol** | Final: 09 February 2018 |
| **Date of protocol amendment** | Amendment 1 Final: 15 May 2018<br>Amendment 2 Final: 29 August 2018 |
| **Title** | Immunogenicity and Safety of Meningococcal MenABCWY Vaccine, and of rMenB+OMV NZ and MenACWY Administered Concomitantly in the Same Arm or in 2 Different Arms, or Alone |
| **Detailed title** | A Phase II, Randomized, Open-label, Multicenter Study to Assess the Immunogenicity and Safety of GSK Meningococcal MenABCWY Vaccine, and of GSK Meningococcal Group B and MenACWY Conjugate Vaccines Administered Concomitantly in the Same Arm or in 2 Different Arms, or Alone in Healthy Subjects 10 to 25 Years of Age |
| **Co-ordinating author** | PPD, Principal Medical Writer, PPD, for GSK Biologicals |
| **Contributing authors** *(Amended 29 Aug 2018)* | • PPD, Clinical Research Development Lead<br>• PPD, Project Statistician<br>• PPD, Lead Statistician<br>• PPD/PPD, Study Delivery Lead<br>• PPD, Study Delivery Associate<br>• PPD, Clinical Trial Supply Manager<br>• PPD, Scientific Writer |

| | |
|---|---|
| **eTrack study number and abbreviated title** | 208205 MENABCWY-016 (V102_19) |
| **EudraCT number** | 2017-005128-12 |
| **Detailed title** | A Phase II, Randomized, Open-label, Multicenter Study to Assess the Immunogenicity and Safety of GSK Meningococcal MenABCWY Vaccine, and of GSK Meningococcal Group B and MenACWY Conjugate Vaccines Administered Concomitantly in the Same Arm or in 2 Different Arms, or Alone in Healthy Subjects 10 to 25 Years of Age |
| **Contributing authors (continued)** | • PPD, Clinical and Epidemiology R&D Project Lead<br>• PPD, Clinical Laboratory Sciences Study Manager<br>• PPD, Clinical Laboratory Sciences Study Manager<br>• PPD, Clinical Laboratory Sciences Read-out Team Leader<br>• PPD/PPD, SERM Safety Scientist, for GSK Biologicals<br>• PPD, Oversight Data Management<br>• PPD, Regulatory Affairs Representative<br>• PPD, Global Patents Representative |

# Protocol Amendment 2 Sponsor Signatory Approval

| | |
|---|---|
| **eTrack study number and abbreviated title** | 208205 MENABCWY-016 (V102_19) |
| **EudraCT number** | 2017-005128-12 |
| **Date of protocol amendment** | Amendment 2 Final: 29 August 2018 |
| **Detailed title** | A Phase II, Randomized, Open-label, Multicenter Study to Assess the Immunogenicity and Safety of GSK Meningococcal MenABCWY Vaccine, and of GSK Meningococcal Group B and MenACWY Conjugate Vaccines Administered Concomitantly in the Same Arm or in 2 Different Arms, or Alone in Healthy Subjects 10 to 25 Years of Age |
| **Sponsor signatory** | Daniela Toneatto, MD<br>Clinical and Epidemiology R&D Project Lead |
| **Signature** | _____ |
| **Date** | _____ |

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# Protocol Amendment 2 Rationale

| | |
|---|---|
| **Amendment number:** | Amendment 2, substantial |

**Rationale/background for changes:**

- A tertiary objective was added to allow potential exploratory evaluation of immune responses induced by the study vaccine(s) against a panel of strains of *Neisseria* species in a subset of subjects.
- Protocol Clarification Letter 1 was incorporated, which removed reference to a pregnancy electronic case report form.
- The window for Subject Diary reminder calls was clarified.
- Other minor changes were made to correct typos, and improve clarity and alignment within the document.

# Protocol Amendment 2 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/PPD.
- 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/PPD 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/PPD will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals/PPD 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 1 year following completion of the study.
- Agree that GSK Biologicals/PPD may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals/PPD with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

| | |
|---|---|
| **eTrack study number and abbreviated title** | 208205 MENABCWY-016 (V102_19) |
| **EudraCT number** | 2017-005128-12 |
| **Date of protocol amendment** | Amendment 2 Final: 29 August 2018 |
| **Detailed title** | A Phase II, Randomized, Open-label, Multicenter Study to Assess the Immunogenicity and Safety of GSK Meningococcal MenABCWY Vaccine, and of GSK Meningococcal Group B and MenACWY Conjugate Vaccines Administered Concomitantly in the Same Arm or in 2 Different Arms, or Alone in Healthy Subjects 10 to 25 Years of Age |
| **Investigator name** | _____ |
| **Signature** | _____ |
| **Date** | _____ |

# 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

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

# SYNOPSIS

| | |
|---|---|
| **Study title** | A Phase II, Randomized, Open-label, Multicenter Study to Assess the Immunogenicity and Safety of GSK Meningococcal MenABCWY Vaccine, and of GSK Meningococcal Group B and MenACWY Conjugate Vaccines Administered Concomitantly in the Same Arm or in 2 Different Arms, or Alone in Healthy Subjects 10 to 25 Years of Age |
| **EudraCT number** | 2017-005128-12 |
| **Study protocol number** | 208205 MENABCWY-016 (V102_19)<br>Final: 09 February 2018<br>Amendment 1 Final: 15 May 2018<br>Amendment 2 Final: 29 August 2018 |
| **Investigational product (primary study vaccine and number)** | GlaxoSmithKline (GSK) Biologicals' meningococcal MenABCWY vaccine (GSK3536819A) |
| **Phase** | II |
| **Rationale for the study** | In previous clinical studies of MenABCWY versus rMenB+OMV NZ, immune responses against serogroup B antigens were lower than immune responses assessed when rMenB+OMV NZ was administered alone. One possible reason that has been theorized is biological immune interference, possibly due to immunological stress to the lymph nodes in the arm where the combination vaccine is administered. The purpose of the current study is to evaluate whether there is immune interference when MenABCWY is administered to healthy adolescents and adults. |
| **Risk/Benefit assessment** | No significant safety signals have been identified for MenABCWY. Cumulative safety data have not identified new important safety risks. The balance of anticipated benefits and apparent risks associated with MenABCWY continues to be acceptable following the ongoing systematic review of safety data.<br><br>Taking into account the measures taken to minimize risk to subjects participating in this study, the potential or identified risks identified in association with rMenB+OMV NZ, MenACWY, and MenABCWY are justified by the potential benefits (prevention/treatment) that may be afforded to subjects. |

| | |
|---|---|
| **Used medicinal products** | **Primary study vaccine**<br>• GSK Biologicals' meningococcal MenABCWY vaccine (GSK3536819A)<br>**Other study vaccines**<br>• GSK Biologicals' meningococcal rMenB+OMV NZ vaccine (*Bexsero*; GSK3536829A)<br>• GSK Biologicals' meningococcal MenACWY vaccine (*Menveo*; GSK3536820A) |
| **Number of subjects** | Target enrollment will be approximately 500 subjects (approximately 100 subjects per group). The sample size is for exploratory statistical analysis purposes only. |
| **Purpose of this clinical study** | This Phase II, randomized, open-label clinical study is designed to evaluate the potential immune interference when MenABCWY is administered to healthy subjects as 2 injections, 2 months apart. |
| **Indication** | Primary immunization against *Neisseria meningitidis* serogroups A, B, C, W-135, and Y. |
| **Objectives** | **Primary**<br>• To assess the immune response to 2 doses of MenABCWY, rMenB+OMV NZ, or rMenB+OMV NZ and MenACWY administered concomitantly in the same arm or in 2 different arms, and to a single dose of MenACWY at 1 month after the last vaccination.<br>**Secondary**<br><u>Immunogenicity Objective</u><br>• To assess the immune response to 2 doses of MenABCWY, rMenB+OMV NZ, or rMenB+OMV NZ and MenACWY administered concomitantly in the same arm or in 2 different arms at 1 month after the first vaccination.<br><u>Safety Objective</u><br>• To assess the safety and tolerability of 2 doses of MenABCWY, rMenB+OMV NZ, or rMenB+OMV NZ and MenACWY administered concomitantly in the same arm or in 2 different arms, and to a single dose of MenACWY. |

***Tertiary***

- ***To further characterize the immune response induced by the study vaccine(s) against an additional panel of strains of Neisseria species in a subset of subjects.***

  ***Note: This tertiary objective is exploratory and suitable assays may or may not be developed. The tertiary objective will be assessed in a subset of subjects using remaining serum after the primary and secondary analyses have been completed; no additional blood samples will be collected from subjects. Any outcome of exploratory testing that would be of scientific/medical relevance will be reported in an annex/addendum to the final study report.***

  ***(Amended 29 Aug 2018)***

**Method of evaluation**

**Primary**

- Immune responses against *N. meningitidis* serogroup B* test strains and *N. meningitidis* serogroups A, C, W-135, and Y, as measured by a serum bactericidal assay using human complement (hSBA), 1 month after the last vaccination in all study groups
  - hSBA geometric mean titers (GMTs) against each of the *N. meningitidis* serogroup B test strains and against *N. meningitidis* serogroups A, C, W-135, and Y
  - hSBA GMTs against all of *N. meningitidis* serogroup B test strains (pooled)
  - Percentage of subjects with hSBA titers ≥ the lower limit of quantitation (LLOQ) against each *N. meningitidis* serogroup B test strains and against *N. meningitidis* serogroups A, C, W-135, and Y
  - Percentage of subjects with a 4-fold increase in hSBA titers against *N. meningitidis* serogroups B test strains and against *N. meningitidis* serogroups A, C, W-135, and Y
  - hSBA geometric mean ratios (GMRs) against each of the *N. meningitidis* serogroup B test strains and against *N. meningitidis* serogroups A, C, W-135, and Y at 1 month after the last vaccination against baseline (Day 1)

*Serogroup B strains that will be tested are M14459 (factor H binding protein; fHbp), 96217 (Neisserial adhesin A; NadA), NZ98/254 (PorA), and M07-0241084 (Neisseria heparin

binding antigen; NHBA) and will be pooled to estimate the effect of immune interference due to stress to lymph nodes.

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 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 4 times the LLOQ; and c) for individuals whose pre-vaccination titers are ≥ the LLOQ, the post-vaccination titers must be at least 4 times the pre-vaccination titer.

**Secondary**

Immunogenicity Endpoints

- Immune responses against *N. meningitidis* serogroup B test strains and *N. meningitidis* serogroups A, C, W-135, and Y, as measured by hSBA, 1 month after the first vaccination in all groups (except for subjects in the MenACWY group)

The statistical analyses and comparisons for the secondary immunogenicity endpoints will be the same as described for the primary endpoint.

Safety Endpoints

- Solicited local and systemic adverse events (AEs) in all study groups
  - Occurrence of solicited local and systemic AEs during the 7 days (including the day of vaccination) after each vaccination (Day 1 to Day 7 and Day 61 to Day 67 [Day 1 to Day 7 only for subjects in the MenACWY group])
- Unsolicited AEs in all study groups
  - Occurrence of unsolicited AEs during the 30 days (including the day of vaccination) after each vaccination (Day 1 to Day 31 and Day 61 to Day 91 [Day 1 to Day 31 only for subjects in the MenACWY group])
- Serious AEs (SAEs), medically attended AEs, AEs leading to withdrawal, and AEs of special interest, in all study groups from informed consent signature to Visit 4 (Day 91)

  Note: Arthritis is the only AE of special interest in this study.

***Tertiary***

***Endpoints related to the tertiary objective will be described in a separate statistical analysis plan. (Amended 29 Aug 2018)***

**Study population**

**Inclusion criteria**

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

1. Subjects and/or subjects' parent(s)/Legally Acceptable Representative(s) (LARs) who, in the opinion of the investigator, can and will comply, with the requirements of the protocol (e.g. completion of the paper diary [pDiary], return for follow-up visits, availability for all visits scheduled in the study).
2. Written informed consent obtained from the subject and/or from the parent(s)/LAR(s) of the subject prior to performing any study specific procedure.
3. Written informed assent obtained from subjects below the legal age of consent prior to performing any study specific procedure.
4. A male or female between, and including, 10 to 25 years of age at the time of the first 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, or bilateral ovariectomy.
7. Female subjects of childbearing potential may be enrolled in the study, if the subject:
   - has practiced highly effective contraception for 30 days prior to vaccination, and
   - has a negative pregnancy test on the day of vaccination, and
   - has agreed to continue highly effective contraception during the entire treatment period and for 2 months after completion of the vaccination series.

**Exclusion criteria**

If ANY exclusion criterion applies, the subject must not be included in the study:

1. Female planning to become pregnant or planning to discontinue contraceptive precautions.
2. Pregnant or lactating female.
3. Child in care.

Each subject must not have:

4. Current or previous, confirmed or suspected disease caused by *N. meningitidis*.
5. Known contact to an individual with any laboratory-confirmed *N. meningitidis* infection within 60 days prior to enrollment.
6. Previous vaccination against *N. meningitidis* at any time prior to informed consent.
7. Progressive, unstable or uncontrolled clinical conditions.
8. Hypersensitivity, including allergy, to any component of vaccines, medicinal products or medical equipment whose use is foreseen in this study.
9. Clinical conditions representing a contraindication to intramuscular (IM) vaccination and blood draws.
10. Abnormal function of the immune system resulting from:
    - Clinical conditions.
    - Systemic administration of corticosteroids (oral/intravenous/IM) for more than 14 consecutive days within 90 days prior to informed consent.
    - Administration of antineoplastic and immune-modulating agents or radiotherapy within 90 days prior to informed consent.
11. Received immunoglobulins or any blood products within 180 days prior to informed consent.
12. Received an investigational or non-registered medicinal product within 30 days prior to informed consent.
13. Any other clinical condition that, in the opinion of the investigator, might interfere with the results of the study or pose additional risk to the subject due to participation in the study.
14. 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).

15. Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic, or renal functional abnormality, as determined by physical examination.
16. Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
17. Are obese at screening (e.g. with a body mass index [BMI] ≥30 kg/$m^2$, where BMI reflects obesity and not high muscle mass).
18. Family history of congenital or hereditary immunodeficiency.
19. History of neuroinflammatory or autoimmune condition.
20. History of significant neurological disorder or seizure (history of febrile convulsion should not lead to exclusion).
21. Serious chronic illness.
22. History of chronic alcohol consumption and/or drug abuse (including current consumption/abuse).
23. Any study personnel as an immediate family or household member.
24. Administration of a vaccine not foreseen by the study protocol in the period starting 14 days (for inactivated vaccines), 28 days (for live vaccines), or 7 days (for influenza vaccines) before each dose and ending 14 days (for inactivated vaccines), 28 days (for live vaccines), or 7 days (for influenza vaccines) after each dose of study vaccine(s) administration.
25. Thrombocytopenia, bleeding disorders, or be receiving anticoagulant therapy.

**Criteria for withdrawal from the study**

From an analysis perspective, a "withdrawal" from the study refers to when a subject does not come back for the concluding visit foreseen in the protocol. A subject is considered "withdrawn" 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. Information relative to the withdrawal will be documented in the electronic case report form (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.

A "withdrawal" from the study vaccine(s) refers to when a subject any subject who does not receive the complete treatment, i.e. when no further planned dose is administered from the date of withdrawal. A subject withdrawn from the study vaccine(s) may not necessarily be withdrawn from the study as further study procedures or follow-up may be performed (safety or immunogenicity) if planned in the study protocol. Information relative to premature discontinuation of the study vaccine(s) will be documented in the eCRF.

Reasons was responsible for withdrawal:

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

**Treatment, Dose level(s)**

See Dosage and Administration Table.

## Synopsis Table 1 Dosage and administration

| Type of contact and time point | Study group | Treatment name | Volume to be administered | Route[1] | Site | | |
|---|---|---|---|---|---|---|---|
| | | | | | Location | Directionality[2] | Laterality[3] |
| Visit 1 (Day 1) | MenABCWY | MenABCWY[4] | 0.5 mL | IM | Deltoid | Upper or lower | Non-dominant |
| | rMenBOMV+ACWY_S[5] | rMenB+OMV NZ | 0.5 mL | | Upper Deltoid (approximately 2.5 cm above MenACWY injection) | Upper | Non-dominant |
| | | MenACWY[6] | 0.5 mL | | Lower Deltoid (approximately 2.5 cm below rMenB+OMV NZ injection) | Lower | Non-dominant |
| | rMenBOMV+ACWY_D[7] | rMenB+OMV NZ | 0.5 mL | | Deltoid | Upper or lower | Non-dominant |
| | | MenACWY[6] | 0.5 mL | | Deltoid | Upper or lower | Dominant |
| | rMenBOMV | rMenB+OMV NZ | 0.5 mL | | Deltoid | Upper or lower | Non-dominant |
| | MenACWY | MenACWY[6] | 0.5 mL | | Deltoid | Upper or lower | Non-dominant |
| Visit 3 (Day 61) | MenABCWY | MenABCWY[4] | 0.5 mL | IM | Deltoid | Upper or lower | Non-dominant |
| | rMenBOMV+ACWY_S[5] | rMenB+OMV NZ | 0.5 mL | | Upper Deltoid (approximately 2.5 cm above MenACWY injection) | Upper | Non-dominant |
| | | MenACWY[6] | 0.5 mL | | Lower Deltoid (approximately 2.5 cm below rMenB+OMV NZ injection) | Lower | Non-dominant |
| | rMenBOMV+ACWY_D[7] | rMenB+OMV NZ | 0.5 mL | | Deltoid | Upper or lower | Non-dominant |
| | | MenACWY[6] | 0.5 mL | | Deltoid | Upper or lower | Dominant |
| | rMenBOMV | rMenB+OMV NZ | 0.5 mL | | Deltoid | Upper or lower | Non-dominant |

[1]Intramuscular (IM)
[2]Directionality is a qualifier for further detailing the location of the vaccine(s) administration (e.g. Upper, Lower)
[3]The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the vaccine(s) in the non-dominant arm, an injection in the dominant arm may be performed.
[4]MenABCWY is to be reconstituted as a 0.5 mL solution between MenACWY lyo (lyophilized component) and rMenB+OMV NZ (liquid component) by trained staff.
[5]S refers to administration in the same arm (approximately 2.5 cm apart).
[6]MenACWY is to be reconstituted as a 0.5 mL solution between Men A lyo (lyophilized component) and Men CWY liquid (liquid component) by trained staff.
[7]D refers to administration in 2 different arms.

| | |
|---|---|
| **Route of administration** | IM |
| **Excluded concomitant medications** | 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.<br>• Any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) used during the study period.<br>• Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 consecutive days in total) during the study period. Inhaled and topical steroids are allowed.<br>• Long-acting immune-modifying drugs administered at any time during the study period (e.g. infliximab).<br>• A vaccine not foreseen by the study protocol administered during the period of 14 days (for in activated vaccines), 28 days (for live vaccines), or 7 days (for influenza vaccines) before or after administration of the study vaccine(s) at Visit 1 and Visit 3.<br>• Drug and/or alcohol abuse that, in the opinion of the investigator, will interfere with the results of the study or pose additional risk to the subject. |
| **Overview of the study design** | This Phase II, randomized, open-label clinical study is designed to evaluate the potential immune interference when MenABCWY is administered to healthy subjects as 2 injections, 2 months apart. To accomplish this aim, immune responses to MenABCWY will be assessed and compared with responses to MenACWY (*Menveo*) and rMenB+OMV (*Bexsero*) when administered concomitantly (in the same arm or in 2 different arms) or either vaccine alone. Immune responses will be measured by hSBA using a standard panel consisting of *N. meningitidis* serogroup A, C, W-135, and Y and serogroup B test strains directed against each of the major corresponding meningococcal antigens included in the vaccines (Men B test strains for rMenB+OMV NZ and Men A, C, W-135, and Y test strains for MenACWY). Concomitant administration of MenACWY and rMenB+OMV NZ vaccines in the same arm (approximately 2.5 cm apart) or in 2 different arms will allow evaluation of a potential immune interference due to immunological stress to lymph nodes in the arm where the combination vaccine is administered. |

**Study design**

- Experimental design: Phase II, open-label, randomized, controlled, multi-centric, study with 5 parallel study groups
- Duration of the study: Up to 91 days (4 visits, 30 days apart)
  - Epoch 001: Starting at Visit 1 (Day 1) and ending at Visit 4 (Day 91)
- Primary Completion Date: Visit 4 (Day 91)
- End of Study: Date of the last testing results released for the samples collected at Visit 4 (Day 91), to be achieved no later than 8 months after the Last Subject Last Visit
- Study groups:

  Approximately 500 subjects will be randomly assigned at a 1:1:1:1:1 ratio to receive one of the following:

  - MenABCWY: Approximately 100 subjects (50 subjects aged 10 to 17 years and 50 subjects aged 18 to 25 years) will receive 1 IM dose of MenABCWY twice, 2 months apart.
  - rMenBOMV+ACWY_S: Approximately 100 subjects (50 subjects aged 10 to 17 years and 50 subjects aged 18 to 25 years) will concomitantly receive 1 IM dose of rMenB+OMV NZ and 1 IM dose of MenACWY in the same arm (approximately 2.5 cm apart) twice, 2 months apart.
  - rMenBOMV+ACWY_D: Approximately 100 subjects (50 subjects aged 10 to 17 years and 50 subjects aged 18 to 25 years) will concomitantly receive 1 IM dose of rMenB+OMV NZ and 1 IM dose of MenACWY in 2 different arms twice, 2 months apart.
  - rMenBOMV: Approximately 100 subjects (50 subjects aged 10 to 17 years and 50 subjects aged 18 to 25 years) will receive 1 IM dose of rMenB+OMV NZ twice, 2 months apart.
  - MenACWY: Approximately 100 subjects (50 subjects aged 10 to 17 years and 50 subjects aged 18 to 25 years) will receive 1 IM dose of MenACWY once.

**Synopsis Table 2 Study groups and epochs foreseen in the study**

| Study groups | Number of subjects[1] | Age (Min – Max) | Epochs |
|---|---|---|---|
| | | | Epoch 001 |
| MenABCWY | 100 | 10 years – 25 years | x |
| rMenBOMV+ACWY_S[2] | 100 | 10 years – 25 years | x |
| rMenBOMV+ACWY_D[3] | 100 | 10 years – 25 years | x |
| rMenBOMV | 100 | 10 years – 25 years | x |
| MenACWY | 100 | 10 years – 25 years | x |

[1]Approximate number of subjects.
[2]S refers to administration in the same arm (approximately 2.5 cm apart).
[3]D refers to administration in 2 different arms.

**Synopsis Table 3 Study groups and treatment foreseen in the study**

| Treatment name | Vaccine name | Study groups | | | | |
|---|---|---|---|---|---|---|
| | | MenABCWY | rMenBOMV +ACWY_S[1] | rMenBOMV +ACWY_D[2] | rMenBOMV | MenACWY |
| MenABCWY | MenACWY lyo | x | | | | |
| | rMenB+OMV NZ | | | | | |
| rMenB+OMV NZ | rMenB+OMV NZ | | x | x | x | |
| MenACWY | MenA lyo | | x | x | | x |
| | MenCWY liquid | | | | | |

[1]S refers to administration in the same arm (approximately 2.5 cm apart).
[2]D refers to administration in 2 different arms.

- Control: active control
- Vaccination schedules: First vaccination at Visit 1 (Day 1) and second vaccination at Visit 3 (Day 61), with the exception of the MenACWY study group, which will have only 1 vaccination at Visit 1 (Day 1)
- Treatment allocation: Randomization will be performed prior to or at Visit 1 (Day 1). The randomization list will be generated using MATerial EXcellence (MATEX). Central randomization will be performed using the Source DataBase for Internet Randomization (SBIR) system.

  Note: Within each age stratum (10 to 17 years and 18 to 25 years) the randomization algorithm will use a minimization procedure accounting for center.
- Blinding: Open-label

**Synopsis Table 4 Blinding of study epochs**

| Study Epochs | Blinding |
|---|---|
| Epoch 001 | Open |

- Sampling schedule: Blood samples of approximately 20 mL will be taken at Visit 1, Visit 2, and Visit 4, with the exception of the MenACWY study group, which will have blood samples collected only at Visit 1 and Visit 2
- Type of study: Self-contained
- Data collection: Standardized eCRF; solicited symptoms will be collected using a subject pDiary

| | |
|---|---|
| **Statistical methodology** | For more information about statistical methodology, see protocol Section 10. |

## Synopsis Table 5 List of study procedures

| Epoch | *Epoch 001* | | | | | |
|---|---|---|---|---|---|---|
| **Type of contact** | **Visit 1** | **Safety call 1** | **Visit 2** | **Visit 3** | **Safety call 2** | **Visit 4** |
| **Time points** | **Day 1** | **Day 15** | **Day 31** | **Day 61** | **Day 75** | **Day 91** |
| **Sampling time points** | **Pre-Vacc 1** | | **Post-Vacc 1** | | | **Post-Vacc 2** |
| Informed consent | ●[1] | | | | | |
| Check inclusion/exclusion criteria | ●[1] | | | ○ | | |
| Collect demographic data | ●[1] | | | | | |
| Medical history | ●[1] | | | | | |
| History directed physical examination | ○ | | | | | |
| Physical examination | ○ | | | ○ | | |
| Urine pregnancy test | ●[2, 3] | | | ●[2,3] | | |
| Check contraindications and warnings and precautions to vaccination | ● | | | ●[4] | | |
| Pre-vaccination body temperature | ● | | | ●[4] | | |
| Measure/record height and weight | ●[1] | | | | | |
| Study group and treatment number allocation | ● | | | | | |
| Recording of administered treatment number | ● | | | ●[4] | | |
| Blood sampling (~20 mL) | ●[5] | | ● | | | ●[4] |
| Vaccine(s) administration | ● | | | ●[4] | | |
| Record any concomitant medications/vaccinations | ● | ● | ● | ●[4] | ●[4] | ●[4] |
| Record any intercurrent medical conditions | ● | ● | ● | ●[4] | ●[4] | ●[4] |
| Distribution of pDiary | ○ | | | ○[4,6] | | |
| Review of pDiary | | | ○ | ○[4] | | ○[4] |
| Return of pDiary | | | ○[6] | ○[4,6] | | ○[4,6] |
| Recording of AEs within 30 minutes post-vaccination | ● | | | ●[4] | | |
| Recording of solicited AEs (days 1 to 7 post-vaccination) | ● | | | ●[4] | | |
| Recording of unsolicited AEs (days 1 to 30 post-vaccination) | ● | ● | ● | ●[4] | ●[4] | ●[4] |
| Recording of AEs, SAEs, medically attended AEs, AESI, and AEs leading to withdrawal | ●[1] | ● | ● | ● | ● | ● |
| Recording of AEs/SAEs related to study participation or to a concurrent GSK medication/vaccine | ●[1] | ● | ● | ● | ● | ● |
| Recording of SAEs related to study vaccine(s) | ●[1] | ● | ● | ● | ● | ● |
| Study conclusion | | | | | | ● |

[1]Activities that can be performed at a separate visit before Visit 1 (maximum 5 days before the Visit 1). All AEs/SAEs, including those related to study participation or to a concurrent GSK medication/vaccine should be recorded starting from informed consent signature. Inclusion/exclusion criteria should be re-checked prior to vaccination at Visit 1.
[2]For women of childbearing age. The pregnancy test is to be performed locally onsite.
[3]A pregnancy test is mandatory even if performed during a prior separate visit.
[4]This study procedure will not be performed at this time point for the MenACWY group, administered only 1 dose of vaccine at Visit 1 (no Visit 3 performed)
[5]Blood sample collection will be performed before vaccine(s) administration.
[6]Subjects who receive a single dose of MenACWY only will return their pDiary at Visit 2 (Day 31). All subjects in the other treatment groups will return their first pDiary at Visit 3 (Day 61) and will receive a second pDiary for the remainder of the study.
● 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.
AE = adverse event; AESI = adverse event of special interest; eCRF = electronic case report form;
GSK = GlaxoSmithKline; Pre-Vacc: pre-vaccination; Post-Vacc: post-vaccination; SAE = serious adverse event

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| ADEM | Acute disseminated encephalomyelitis |
| AE | Adverse event |
| AESI | Adverse events of special interest |
| ANCOVA | Analysis of covariance |
| ATEAM | Advanced Temperature Excursion Analysis and Management |
| BMI | Body mass index |
| CFS | Chronic fatigue syndrome |
| CI | Confidence interval |
| eCRF | Electronic case report form |
| EoS | End of Study |
| EU | European Union |
| FAS | Full Analysis Set |
| fHbp | Factor H binding protein |
| GBS | Guillain-Barré Syndrome |
| GCP | Good Clinical Practice |
| GMR | Geometric mean ratio |
| GMT | Geometric mean titer |
| GSK | GlaxoSmithKline |
| hSBA | Serum bactericidal assay using human complement |
| IAF | Informed assent form |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation |
| IM | Intramuscular(ly) |
| IMD | Invasive meningococcal disease |

| | |
|---|---|
| LAR | Legally Acceptable Representative |
| LLOQ | Lower limit of quantitation |
| LOD | Limit of detection |
| LSLV | Last Subject Last Visit |
| MATEX | MATerial EXcellence |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NadA | Neisserial adhesin A |
| NHBA | Neisseria heparin binding antigen |
| OMV | Outer membrane vesicles |
| PCD | Primary Completion Date |
| pDiary | Paper diary |
| PPS | Per-Protocol Set |
| SD | Standard deviation |
| SAE | Serious adverse event |
| SBIR | Source DataBase for Internet Randomization |
| SmPC | Summary of Product Characteristics |
| SPM | Study Procedures Manual |
| US | United States |

# GLOSSARY OF TERMS

| | |
|---|---|
| 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.<br><br>An adverse event (AE) can therefore be any unfavorable 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. |
| Adverse events of special interest: | Adverse events of special interest (AESIs): are predefined (serious or non-serious) adverse events of scientific and medical concern specific to the product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate, because such an event might warrant further investigation in order to characterize and understand it. |
| 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 open-label study, no blind is used. Both the investigator and the subject know the identity of the treatment assigned. |
| 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 with collection of Human Biologicals Samples or imaging data, End of Study (EoS) is defined as the date of the last testing/reading released of the Human Biological Samples or imaging data, related to primary and secondary endpoints. EoS must be achieved no later than 8 months after the Last Subject Last Visit (LSLV). |
| Epoch: | An epoch is a set of consecutive time points or a single time point 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 time points included in an epoch must be sufficient to fulfil the purpose of the epoch.<br><br>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. |
| Highly effective contraception: | Highly effective contraceptive methods, defined as contraceptive methods with a failure rate of less than 1% per year according to the Pearl Index, when used consistently and correctly and in accordance with the product label, when applicable. These methods include:<br>• combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:<br>  • oral<br>  • intravaginal (i.e. contraceptive vaginal ring)<br>  • percutaneous delivery system (i.e. transdermal patch)<br>• progestogen-only hormonal contraception associated with inhibition of ovulation:<br>  • injectable<br>  • implantable<br>• intrauterine device<br>• intrauterine hormone-releasing system<br>• bilateral tubal occlusion |

| | |
|---|---|
| | • vasectomized partner (provided that partner is the sole sexual partner of the female subject and that the vasectomized partner has received medical assessment of the surgical success, i.e. documented sterility). The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination of the subject and/or semen analysis, or medical history interview provided by her or her partner.<br>• sexual abstinence (defined as refraining from penile-vaginal intercourse during the entire period of risk associated with the study treatments). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.<br>Highly effective 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. |
| 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. |
| Medically-attended adverse event: | Symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a health care provider. |

| | |
|---|---|
| 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 to 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). |
| 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. |
| Protocol amendment: | The International Council for Harmonisation (ICH) defines a protocol amendment as: "A written description of a change(s) to or formal clarification of a protocol." GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study. |
| Protocol administrative change: | A protocol administrative change addresses changes to only logistical or administrative aspects of the study. |
| 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: | Adverse events 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. |
| Subset: (Synonym of Immunosubset) | Selection of blood samples among all blood samples collected at given time point(s) for testing by specific assay. |
| 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 without the superscript symbol ™ or ® and in *italics*.

| Trademarks of the GSK group of companies | Generic description |
|---|---|
| Bexsero | *Neisseria meningitidis* serogroup B vaccine |
| Menveo | *Neisseria meningitidis* serogroups ACWY conjugate vaccine |

# 1. INTRODUCTION

## 1.1. Background

GlaxoSmithKline (GSK) Biologicals is developing a combination vaccine intended for primary immunization against *Neisseria meningitidis* serogroups A, B, C, W-135, and Y (MenABCWY vaccine). The availability of a meningococcal vaccine based on the combination of antigens in 2 separate vaccines against serogroups ACWY (*Menveo*) and B (*Bexsero*) in a single vaccine/administration would reduce the number of injections and allow greater flexibility in dose administration schedules, and could increase coverage for meningococcal disease caused by *N. meningitidis* serogroups A, B, C, W-135, and Y worldwide.

Please refer to the current Investigator Brochure for information regarding the pre-clinical and clinical studies for MenABCWY.

## 1.2. Rationale for the study and study design

### 1.2.1. Rationale for the study

Invasive meningococcal disease (IMD) occurs when, following an average incubation period of 4 days (range: 2 to 10 days), the normally asymptomatically carried encapsulated gram-negative bacterium *N. meningitidis* enters the bloodstream and multiplies, potentially causing sepsis. If the bacteria cross the blood-brain barrier, meningitis occurs. Sepsis and meningitis caused by *N. meningitidis* are serious diseases that can be fatal or leave permanent sequelae. In European Union (EU)/European Economic Area countries, despite the availability of advanced medical treatment and effective antibiotics, case-fatality rates are high at approximately 7% to 15%, with most cases caused by serogroup B [ECDC, 2016]. Up to one fifth of survivors suffer long-term sequelae, including mental retardation, hearing loss, and loss of limb use [Rosenstein, 2001].

MenACWY is a meningococcal oligosaccharide conjugate vaccine licensed for active immunization to prevent IMD caused by *N. meningitidis* serogroups A, C, W-135, and Y. It is approved for adolescents and adults in more than 60 countries; many of these countries have also approved its use in children. In the EU, the vaccine is indicated for use in individuals 2 years of age and older, and in the United States (US), in individuals 2 months to 55 years of age. Through 14-MAR-2017, more than 31,500 subjects across all age groups were exposed to MenACWY in clinical trials, and more than 28 million individuals were estimated to have been exposed to the vaccine within the post-marketing setting.

The rMenB+OMV NZ vaccine is approved for use in the EU, US, and several other countries for active immunization to prevent IMD caused by *N. meningitidis* serogroup B. In the EU, the vaccine is indicated for use in individuals 2 months of age and older; in the US, in individuals 10 to 25 years of age. Through 13-JAN-2017, more than 13,500 subjects across all age groups were exposed to all formulations of meningococcal group B vaccine in clinical trials. The vaccination course with meningococcal group B

vaccine can vary between 2 and 4 doses per subject depending on age. Thus, post-marketing cumulative subject exposure since the first launch up to 13-JAN-2017 was estimated as being between a minimum of 3,569,743 and a maximum of 7,139,487.

The investigational MenABCWY combination vaccine is based upon the 2 aforementioned and well established GSK Biologicals' vaccines, MenACWY and rMenB+OMV NZ. Both of these vaccines have been extensively tested in clinical trials in order to support marketing authorizations in several jurisdictions.

The clinical development program of the investigational MenABCWY combination vaccine has included 1 Phase I trial, 7 Phase II trials, and 2 Phase IIb trials. In the recent Phase IIb study MenABCWY-011 (V102_15), non-inferiority in terms of geometric mean titers (GMTs) could not be shown for 2 doses of MenABCWY versus 2 doses of rMenB+OMV NZ, given 2 months apart. Across several other studies of the MenABCWY program, immune responses against serogroup B antigens were also lower than immune responses assessed when rMenB+OMV NZ was administered alone. One possible reason that has been theorized is biological immune interference, possibly due to immunological stress to the lymph nodes in the arm where the combination vaccine is administered. The purpose of the current study is to evaluate whether there is immune interference when MenABCWY (consisting of MenACWY lyophilized component and rMenB+OMV NZ liquid component) is administered to healthy adolescents and adults following a 2-dose vaccination schedule with MenABCWY administered 2 months apart.

### 1.2.2. Rationale for the study design

This Phase II, randomized, open-label clinical study is designed to evaluate the potential immune interference when MenABCWY is administered to healthy subjects as 2 injections, 2 months apart. To accomplish this aim, immune responses to MenABCWY will be assessed and compared with responses to MenACWY and rMenB+OMV when administered concomitantly (in the same arm or in 2 different arms) or either vaccine alone. Immune responses will be measured by a serum bactericidal assay using human complement (hSBA) using a standard panel consisting of *N. meningitidis* serogroup A, C, W-135, and Y and serogroup B test strains directed against each of the major corresponding meningococcal antigens included in the vaccines (Men B test strains for rMenB+OMV NZ and Men A, C, W-135, and Y test strains for MenACWY). Concomitant administration of MenACWY and rMenB+OMV NZ vaccines in the same arm (approximately 2.5 cm apart) or in 2 different arms will allow evaluation of a potential immune interference due to immunological stress to lymph nodes in the arm where the combination vaccine is administered.

## 1.3. Benefit:Risk assessment

Please refer to the current Investigator Brochure for the summary of potential risks and benefits of MenABCWY. Please refer to the Summary of Product Characteristics (SmPC) for information regarding the summary of potential risks and benefits of MenACWY and rMenB+OMV NZ.

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 |
|---|---|---|
| Investigational vaccine: ***MenABCWY*** | | |
| Important potential risk: **Anaphylaxis, anaphylactic shock** | Anaphylaxis and anaphylactic shock have been observed with other vaccines. No cases of anaphylaxis related to MenABCWY have been reported in the MenABCWY clinical development program. Allergic reaction (including anaphylactic reaction) is listed in the MenABCWY Investigator Brochure. | Anaphylaxis following the administration of MenABCWY constitutes an absolute contraindication to subsequent vaccination (see Section 6.5). 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 (see Section 5.6.11). |
| Investigational vaccine: ***rMenB+OMV NZ*** | | |
| Important identified risk: **Fever** | Fever may occur following vaccination. Fever is listed in the rMenB+OMV NZ SmPC. | Any febrile illness constitutes a contraindication to administration of the vaccine at the time scheduled for vaccination (see Section 6.5). Prophylactic use of analgesic/antipyretic medications (preferably paracetamol) during the first 7 days after vaccination is allowed on a voluntary basis, but must be recorded in the source document and Concomitant Medications electronic case report form (eCRF) field (see Section 6.7.1). |
| Important potential risk: **Guillain-Barré Syndrome (GBS)** | GBS has been observed with other vaccines. No cases related to this important potential risk have been identified in the rMenB+OMV NZ clinical development program. | GBS will be monitored through serious adverse event (SAE) collection. |
| Important potential risk: **Acute disseminated encephalomyelitis (ADEM)** | ADEM has been observed with other vaccines. No cases have been identified in the rMenB+OMV NZ clinical development program. | ADEM will be monitored through SAE collection. |

| Important potential/identified risk | Data/Rationale for risk | Mitigation strategy |
|---|---|---|
| Important potential risk: **Chronic fatigue syndrome (CFS)** | No cases of CFS have been reported from clinical trials nor from post-marketing experience with rMenB+OMV NZ. A potential concern was raised with CFS following the vaccination with MenBvac (another outer membrane vesicles [OMV] vaccine) in Norway. The results of a case-control study showed no increased risk [Magnus, 2009]. | No specific mitigation in this study. SAE collection is part of the study protocol. |
| Important potential risk: **Anaphylaxis and anaphylactic shock** | No cases of anaphylaxis related to rMenB+OMV NZ have been reported in the rMenB+OMV NZ clinical development program. However, 1 related case of anaphylaxis within 30 minutes post-vaccination was reported in a third party expanded access program (V72_70TP). Allergic reactions (including anaphylactic reactions) are listed (see SmPC). | Anaphylaxis following the administration of rMenB+OMV NZ constitutes an absolute contraindication to subsequent vaccination (see Section 6.5). 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 (see Section 5.6.11). |
| Important potential risk: **Decrease of immunogenicity secondary to prophylactic use of paracetamol** | Prophylactic use of paracetamol reduces the incidence and severity of fever without affecting the immunogenicity of either rMenB+OMV NZ or routine vaccines [Prymula, 2014]. The effect of antipyretics other than paracetamol on the immune response has not been studied. | Prophylactic use of analgesic/antipyretic medications (preferably paracetamol) to reduce febrile reactions during the first 7 days after vaccination is allowed on a voluntary basis, but must be recorded in the source document and Concomitant Medications eCRF field (see Section 6.7.1). |

| Important potential/identified risk | Data/Rationale for risk | Mitigation strategy |
|---|---|---|
| Important potential risk: **Arthritis** | This risk is based on a signal observed for rMenB+OMV NZ. Attenuated live virus vaccines (rubella) have been reported to be associated with joint-related diseases [Tingle, 1986]. Among inactivated vaccines, different manifestations of arthritis following hepatitis B vaccination (psoriatic arthritis, reactive arthritis, etc.) have been described [IOM, 2011]. However, there has been no association of arthritis with meningococcal vaccines reported in the literature. One clinical case of juvenile idiopathic arthritis possibly related to rMenB+OMV NZ and 6 spontaneous reports considered to have a possible causal relationship have been observed. | Arthritis will be monitored through Adverse Events of Special Interest (AESI) collection (see Section 8.1.6.1). |
| Investigational vaccine: ***MenACWY*** | | |
| Important potential risk: **Reconstitution errors** | Cases describing medication errors due to administration of the serogroup CWY vaccine component only without addition of the lyophilized serogroup have been reported during the MenACWY clinical development program. | See Section 6.1. |
| Important potential risk: **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: **ADEM** | ADEM has been observed with other vaccines. Two cases from clinical trials and 5 cases from spontaneous reporting were retrieved from the GSK's global safety database. None have 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 have 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. No cases of facial paresis were reported from interventional clinical trials. | No specific risk mitigation in place in this study. |
| Important potential risk: **Vaccination failure (lack of efficacy)** | It is known that a protective immune response may not be generated in every recipient. The number of reports suggestive of vaccination failure reported cumulatively does not suggest a significantly or unexpectedly high rate of vaccine failure. | No specific risk mitigation in place in this study. |

| Important potential/identified risk | Data/Rationale for risk | Mitigation strategy |
|---|---|---|
| Study Procedures | | |
| **Risk of blood sampling** | Blood sampling is associated with a risk of syncope, dizziness, and infection after or during venipuncture. | Blood samples will be obtained by a trained professional and medical assistance will be available. The amount of blood to be taken for sampling will not be harmful to the health of the subject. |

### 1.3.2. Benefit assessment

Benefit considerations include:

- Medical evaluations/assessments associated with this study (e.g. physical examinations).
- Contributing to the process of developing new therapies in an area of unmet need.
- Potential benefit of receiving the licensed rMenB+OMV NZ and MenACWY vaccines.

### 1.3.3. Overall benefit : risk conclusion

No significant safety signals have been identified for MenABCWY. Cumulative safety data have not identified new important safety risks. The balance of anticipated benefits and apparent risks associated with MenABCWY continues to be acceptable following the ongoing systematic review of safety data.

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential or identified risks identified in association with rMenB+OMV NZ, MenACWY, and MenABCWY are justified by the potential benefits (prevention/treatment) that may be afforded to subjects.

# 2. OBJECTIVES

## 2.1. Primary objective

- To assess the immune response to 2 doses of MenABCWY, rMenB+OMV NZ, or rMenB+OMV NZ and MenACWY administered concomitantly in the same arm or in 2 different arms, and to a single dose of MenACWY at 1 month after the last vaccination.

Refer to Section 10.1 for the definition of the primary endpoint.

## 2.2. Secondary objectives

Immunogenicity Objective

- To assess the immune response to 2 doses of MenABCWY, rMenB+OMV NZ, or rMenB+OMV NZ and MenACWY administered concomitantly in the same arm or in 2 different arms at 1 month after the first vaccination.

Safety Objective

- To assess the safety and tolerability of 2 doses of MenABCWY, rMenB+OMV NZ, or rMenB+OMV NZ and MenACWY administered concomitantly in the same arm or in 2 different arms, and to a single dose of MenACWY.

Refer to Section 10.2 for the definition of the secondary endpoints.

## *2.3. Tertiary objective*

- ***To further characterize the immune response induced by the study vaccine(s) against an additional panel of strains of Neisseria species in a subset of subjects.***

***Note: This tertiary objective is exploratory and suitable assays may or may not be developed. The tertiary objective will be assessed in a subset of subjects using remaining serum after the primary and secondary analyses have been completed; no additional blood samples will be collected from subjects. Any outcome of exploratory testing that would be of scientific/medical relevance will be reported in an annex/addendum to the final study report.***

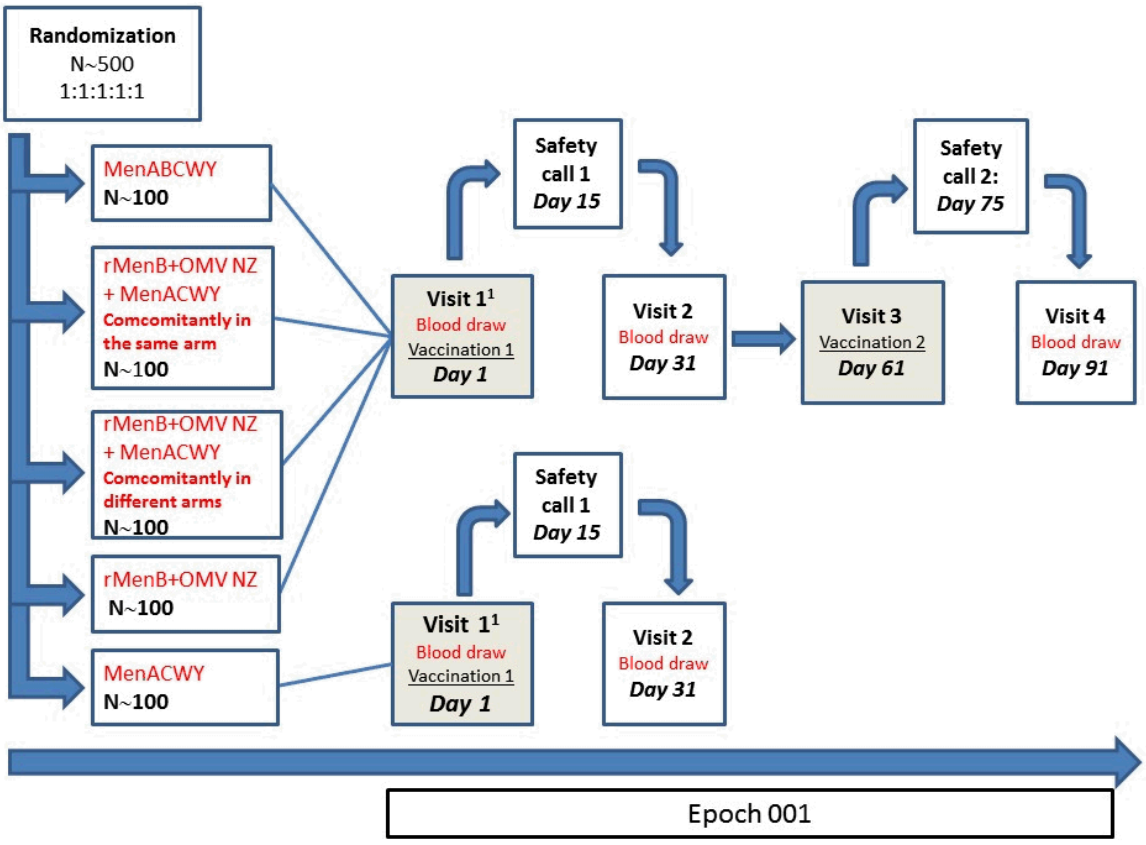
***Refer to Section 10.3 for the definition of the tertiary endpoint and to Section 10.11.1 for the reporting of tertiary endpoint results.***

***(Amended 29 Aug 2018)***

# 3. STUDY DESIGN OVERVIEW

The study design diagram is provided in Figure 1.

**Figure 1 Study design diagram**




A list of procedures that may be performed before Visit 1 is detailed in Table 4.

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 II, open-label, randomized, controlled, multi-centric, study with 5 parallel study groups
- Duration of the study: Up to 91 days (4 visits, 30 days apart)
  - Epoch 001: Starting at Visit 1 (Day 1) and ending at Visit 4 (Day 91)
- Primary Completion Date (PCD): Visit 4 (Day 91)

  Refer to glossary of terms for the definition of PCD.
- End of Study (EoS): Date of the last testing results released for the samples collected at Visit 4 (Day 91), to be achieved no later than 8 months after the Last Subject Last Visit (LSLV)

  Refer to glossary of terms for the definition of EoS.

- Study groups:

  Approximately 500 subjects will be randomly assigned at a 1:1:1:1:1 ratio to receive one of the following:

  – MenABCWY: Approximately 100 subjects (50 subjects aged 10 to 17 years and 50 subjects aged 18 to 25 years) will receive 1 intramuscular (IM) dose of MenABCWY twice, 2 months apart.

  – rMenBOMV+ACWY_S: Approximately 100 subjects (50 subjects aged 10 to 17 years and 50 subjects aged 18 to 25 years) will concomitantly receive 1 IM dose of rMenB+OMV NZ and 1 IM dose of MenACWY in the same arm (approximately 2.5 cm apart) twice, 2 months apart.

  – rMenBOMV+ACWY_D: Approximately 100 subjects (50 subjects aged 10 to 17 years and 50 subjects aged 18 to 25 years) will concomitantly receive 1 IM dose of rMenB+OMV NZ and 1 IM dose of MenACWY in 2 different arms twice, 2 months apart.

  – rMenBOMV: Approximately 100 subjects (50 subjects aged 10 to 17 years and 50 subjects aged 18 to 25 years) will receive 1 IM dose of rMenB+OMV NZ twice, 2 months apart.

  – MenACWY: Approximately 100 subjects (50 subjects aged 10 to 17 years and 50 subjects aged 18 to 25 years) will receive 1 IM dose of MenACWY once.

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

| Study groups | Number of subjects[1] | Age (Min – Max) | Epochs |
|---|---|---|---|
| | | | Epoch 001 |
| MenABCWY | 100 | 10 years – 25 years | x |
| rMenBOMV+ACWY_S[2] | 100 | 10 years – 25 years | x |
| rMenBOMV+ACWY_D[3] | 100 | 10 years – 25 years | x |
| rMenBOMV | 100 | 10 years – 25 years | x |
| MenACWY | 100 | 10 years – 25 years | x |

[1]Approximate number of subjects.
[2]S refers to administration in the same arm (approximately 2.5 cm apart).
[3]D refers to administration in 2 different arms.

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

| Treatment name | Vaccine name | Study groups | | | | |
|---|---|---|---|---|---|---|
| | | MenABCWY | rMenBOMV +ACWY_S[1] | rMenBOMV +ACWY_D[2] | rMenBOMV | MenACWY |
| MenABCWY | MenACWY lyo<br>rMenB+OMV NZ | x | | | | |
| rMenB+OMV NZ | rMenB+OMV NZ | | x | x | x | |
| MenACWY | MenA lyo<br>MenCWY liquid | | x | x | | x |

[1]S refers to administration in the same arm (approximately 2.5 cm apart).
[2]D refers to administration in 2 different arms.

- Control: active control
- Vaccination schedules: First vaccination at Visit 1 (Day 1) and second vaccination at Visit 3 (Day 61), with the exception of the MenACWY study group, which will have only 1 vaccination at Visit 1 (Day 1)
- Treatment allocation: Randomization will be performed prior to or at Visit 1 (Day 1). The randomization list will be generated using MATerial EXcellence (MATEX). Central randomization will be performed using the Source DataBase for Internet Randomization (SBIR) system.
- Blinding: Open-label

**Table 3 Blinding of study epochs**

| Study Epochs | Blinding |
|---|---|
| Epoch 001 | Open |

- Sampling schedule: Blood samples of approximately 20 mL will be taken at Visit 1, Visit 2, and Visit 4, with the exception of the MenACWY study group, which will have blood samples collected only at Visit 1 and Visit 2
- Type of study: Self-contained
- Data collection: Standardized eCRF; solicited symptoms will be collected using a subject paper diary (pDiary)

# 4. STUDY COHORT

## 4.1. Number of subjects/centers

The target enrollment will be approximately 500 subjects (approximately 100 subjects per study group). Refer to Section 10.3 for a detailed description of the criteria used in the determination of sample size.

Overview of the recruitment plan:

- This is a multicenter study.
- Enrollment will be terminated when approximately 500 subjects have been enrolled.
- The recruitment and randomization will be monitored by SBIR.

## 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 and/or subjects' parent(s)/Legally Acceptable Representative(s) (LARs) who, in the opinion of the investigator, can and will comply, with the requirements of the protocol (e.g. completion of the pDiary, return for follow-up visits, availability for all visits scheduled in the study).
2. Written informed consent obtained from the subject and/or from the parent(s)/LAR(s) of the subject prior to performing any study specific procedure.
3. Written informed assent obtained from subjects below the legal age of consent prior to performing any study specific procedure.
4. A male or female between, and including, 10 to 25 years of age at the time of the first 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, or bilateral ovariectomy.

Please refer to the glossary of terms for the definition of menarche.

7. Female subjects of childbearing potential may be enrolled in the study, if the subject:
   - has practiced highly effective for 30 days prior to vaccination, and
   - has a negative pregnancy test on the day of vaccination, and
   - has agreed to continue highly effective contraception during the entire treatment period and for 2 months after completion of the vaccination series.

Please refer to the glossary of terms for the definition of highly effective 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. Female planning to become pregnant or planning to discontinue contraceptive precautions.
2. Pregnant or lactating female.
3. Child in care.

   Please refer to the glossary of terms for the definition of child in care.

Each subject must not have:

4. Current or previous, confirmed or suspected disease caused by *N. meningitidis*.

5. Known contact to an individual with any laboratory-confirmed *N. meningitidis* infection within 60 days prior to enrollment.
6. Previous vaccination against *N. meningitidis* at any time prior to informed consent.
7. Progressive, unstable or uncontrolled clinical conditions.
8. Hypersensitivity, including allergy, to any component of vaccines, medicinal products or medical equipment whose use is foreseen in this study.
9. Clinical conditions representing a contraindication to IM vaccination and blood draws.
10. Abnormal function of the immune system resulting from:
    - Clinical conditions.
    - Systemic administration of corticosteroids (oral/intravenous/IM) for more than 14 consecutive days within 90 days prior to informed consent.
    - Administration of antineoplastic and immune-modulating agents or radiotherapy within 90 days prior to informed consent.
11. Received immunoglobulins or any blood products within 180 days prior to informed consent.
12. Received an investigational or non-registered medicinal product within 30 days prior to informed consent.
13. Any other clinical condition that, in the opinion of the investigator, might interfere with the results of the study or pose additional risk to the subject due to participation in the study.
14. 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).
15. Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic, or renal functional abnormality, as determined by physical examination.
16. Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
17. Are obese at screening (e.g. with a body mass index [BMI] ≥30 kg/$m^2$, where BMI reflects obesity and not high muscle mass).
18. Family history of congenital or hereditary immunodeficiency.
19. History of neuroinflammatory or autoimmune condition.
20. History of significant neurological disorder or seizure (history of febrile convulsion should not lead to exclusion).
21. Serious chronic illness.
22. History of chronic alcohol consumption and/or drug abuse (including current consumption/abuse).
23. Any study personnel as an immediate family or household member.

24. Administration of a vaccine not foreseen by the study protocol in the period starting 14 days (for inactivated vaccines), 28 days (for live vaccines), or 7 days (for influenza vaccines) before each dose and ending 14 days (for inactivated vaccines), 28 days (for live vaccines), or 7 days (for influenza vaccines) after each dose of study vaccine(s) administration.

25. Thrombocytopenia, bleeding disorders, or be receiving anticoagulant therapy.

# 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 International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (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 Harmonised Tripartite Guideline for clinical investigation of medicinal products in the pediatric population (ICH E11) and all other applicable ethical guidelines.

PPD, the contract research organization for this study, will obtain favorable 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/Independent Ethics Committee review and favorable opinion/approval of study protocol and any subsequent amendments.
- Subject/subject's parent(s)/LAR(s) informed consent and subject informed assent, as appropriate.
- Investigator reporting requirements as stated in the protocol.

PPD 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.

PPD 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 Harmonised Tripartite Guidelines for GCP, those subjects who can only be enrolled in the study with the consent of the subject's parent(s)/LAR(s) (e.g. minors), should be informed about the study to the extent compatible with the subject's understanding and the subject should sign and personally date a written informed assent form (IAF). It is required that the assent be signed by each subject in addition to the informed consent that is to be signed by his/her parent(s)/LAR(s).

PPD 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 PPD and be approved (along with the protocol, and any other necessary documentation) by the Institutional Review Board/Independent Ethics Committee and other regulatory bodies as applicable.

## 5.2. Subject identification and randomization

### 5.2.1. Subject identification

Subject identification numbers will be assigned sequentially to the subjects who have consented or provided assent with consent from each subject's parent(s)/LAR(s) 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. Treatment allocation to the subject

The treatment numbers will be allocated by dose.

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

The target will be to enroll approximately 500 eligible subjects who will be randomly assigned to 5 study groups in a (1:1:1:1:1) ratio (approximately 100 subjects in each study group).

The enrollment will be performed to ensure equal distribution of the population across the 2 age strata of 10 to 17 years and 18 to 25 years in each study group (i.e., of the approximately 100 subjects in each study group, approximately 50 subjects will be aged 10 to 17 years and approximately 50 subjects will be aged 18 to 25 years).

The randomization list will be generated using MATEX, a program developed by GSK for use in SAS. Central randomization will be performed using SBIR.

Allocation of the subject to a study group at the investigator site will be performed using the SBIR system. Within each age stratum (10 to 17 years and 18 to 25 years), the randomization algorithm will use a minimization procedure accounting for center. Minimization factors will have equal weight in the minimization algorithm.

After obtaining the signed and dated ICF/IAF from the subject/subject's parent(s)/LAR(s) and having checked the eligibility of the subject, the study staff in charge of the vaccine(s) administration will access SBIR. Upon providing the age (10 to 17 years and 18 to 25 years) and the subject identification number, the randomization system will determine the study group and will provide the treatment number to be used for each dose.

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

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

After the target of 50 subjects per age group stratification (10 to 17 years or 18 to 25 years) has been reached in any of the 5 study groups, the enrollment will be frozen for that age and study group.

#### *5.2.2.1.2. Treatment number allocation for subsequent doses*

For each dose subsequent to the first dose, the study staff in charge of the vaccine(s) administration will access SBIR, provide the subject identification number, and the system will provide a treatment number consistent with the allocated study group.

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

## 5.3. Method of blinding

This will be an open-label study.

The laboratory in charge of the laboratory testing will be blinded to the treatment, 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.

## 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

Refer to the list of study procedures in Table 4.

## Table 4 List of study procedures

| Epoch | *Epoch 001* | | | | | |
|---|---|---|---|---|---|---|
| **Type of contact** | **Visit 1** | **Safety call 1** | **Visit 2** | **Visit 3** | **Safety call 2** | **Visit 4** |
| **Time points** | **Day 1** | **Day 15** | **Day 31** | **Day 61** | **Day 75** | **Day 91** |
| **Sampling time points** | **Pre-Vacc 1** | | **Post-Vacc 1** | | | **Post-Vacc 2** |
| Informed consent | ●[1] | | | | | |
| Check inclusion/exclusion criteria | ●[1] | | | ○ | | |
| Collect demographic data | ●[1] | | | | | |
| Medical history | ●[1] | | | | | |
| History directed physical examination | ○ | | | | | |
| Physical examination | ○ | | | ○ | | |
| Urine pregnancy test | ●[2, 3] | | | ●[2,3] | | |
| Check contraindications and warnings and precautions to vaccination | ● | | | ●[4] | | |
| Pre-vaccination body temperature | ● | | | ●[4] | | |
| Measure/record height and weight | ●[1] | | | | | |
| Study group and treatment number allocation | ● | | | | | |
| Recording of administered treatment number | ● | | | ●[4] | | |
| Blood sampling (~20 mL) | ●[5] | | ● | | | ●[4] |
| Vaccine(s) administration | ● | | | ●[4] | | |
| Record any concomitant medications/vaccinations | ● | ● | ● | ●[4] | ●[4] | ●[4] |
| Record any intercurrent medical conditions | ● | ● | ● | ●[4] | ●[4] | ●[4] |
| Distribution of pDiary | ○ | | | ○[4,6] | | |
| Review of pDiary | | | ○ | ○[4] | | ○[4] |
| Return of pDiary | | | ○[6] | ○[4,6] | | ○[4,6] |
| Recording of AEs within 30 minutes post-vaccination | ● | | | ●[4] | | |
| Recording of solicited AEs (days 1 to 7 post-vaccination) | ● | | | ●[4] | | |
| Recording of unsolicited AEs (days 1 to 30 post-vaccination) | ● | ● | ● | ●[4] | ●[4] | ●[4] |
| Recording of AEs, SAEs, medically attended AEs, AESI, and AEs leading to withdrawal | ●[1] | ● | ● | ● | ● | ● |
| Recording of AEs/SAEs related to study participation or to a concurrent GSK medication/vaccine | ●[1] | ● | ● | ● | ● | ● |
| Recording of SAEs related to study vaccine(s) | ●[1] | ● | ● | ● | ● | ● |
| Study conclusion | | | | | | ● |

[1]Activities that can be performed at a separate visit before Visit 1 (maximum 5 days before the Visit 1). All AEs/SAEs, including those related to study participation or to a concurrent GSK medication/vaccine should be recorded starting from informed consent signature. Inclusion/exclusion criteria should be re-checked prior to vaccination at Visit 1.
[2]For women of childbearing age. The pregnancy test is to be performed locally onsite.
[3]A pregnancy test is mandatory even if performed during a prior separate visit.
[4]This study procedure will not be performed at this time point for the MenACWY group, administered only 1 dose of vaccine at Visit 1 (no Visit 3 performed)
[5]Blood sample collection will be performed before vaccine(s) administration.
[6]Subjects who receive a single dose of MenACWY only will return their pDiary at Visit 2 (Day 31). All subjects in the other treatment groups will return their first pDiary at Visit 3 (Day 61) and will receive a second pDiary for the remainder of the study.
● 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.
AE = adverse event; AESI = adverse event of special interest; eCRF = electronic case report form; GSK = GlaxoSmithKline; Pre-Vacc: pre-vaccination; Post-Vacc: post-vaccination; SAE = serious adverse event

Whenever possible, the investigator should arrange study visits within the interval described in Table 5.

**Table 5 Intervals between study visits**

| Interval | Optimal length of interval | Allowed interval (Min – Max)[1] |
|---|---|---|
| Visit 1 (Day 1) → Safety call 1 (Day 15) | 14 days | 11 days – 17 days (Days 12 – 18) |
| Visit 1 (Day 1) → Visit 2 (Day 31) | 30 days | 23 days – 40 days (Days 24 – 41) |
| Visit 1 (Day 1) → Visit 3 (Day 61) | 60 days | 53 days – 70 days (Days 54 – 71) |
| Visit 3 (Day 61) → Safety call 2 (Day 75) | 14 days | 11 days – 17 days (Days 72 – 78) |
| Visit 3 (Day 61) → Visit 4 (Day 91) | 30 days | 23 days – 40 days (Days 84 – 101) |

[1]Safety call time intervals will not be used for the assessment of protocol deviations. The Study Day ranges shown in the table are based on optimal intervals; the actual Study Day ranges for Safety Call 2 and Visit 4 will be based on when Visit 3 occurs.

## 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 4.3 before enrollment.

### 5.6.3. Collect demographic data

Record demographic data such as date of birth (year only), gender, and ethnic origin in the subject's eCRF.

### 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 first study vaccination in the eCRF.

### 5.6.5. Physical examination

Perform a history directed physical examination. This is a physical examination that will include measurement of heart rate, blood pressure, and temperature (preferably axilla). If the investigator determines that the subject's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled.

Physical examination at each study visit subsequent to the first vaccination 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.

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. Pregnancy test

Female subjects of childbearing potential are to have a urine pregnancy test prior to any study vaccine(s) administration. The study vaccine(s) 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.

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

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

### 5.6.8. Assess pre-vaccination body temperature

The body temperature (preferably axilla) of each subject needs to be measured prior to any study vaccine(s) administration. If the subject has a fever (fever is defined as temperature ≥38.0°C regardless the location of measurement) on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit as described in Table 5.

### 5.6.9. 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 subject records and the eCRF.

### 5.6.10. Sampling

Please refer to the Biospecimen Management section of the SPM and the central laboratory manual for detailed instructions for the collection, handling, processing, storage, and shipment of the samples.

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

Blood samples will be taken during certain study visits as specified in Section 5.5 outline 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 time point. After centrifugation, serum samples should be kept at -20°C or below until shipment. Refer to the SPM and the central laboratory manual for details.
- An overall volume of up to approximately 60 mL will be collected during the entire study period for immune response assessments, with the exception of the MenACWY study group, which will have an overall volume of approximately 40 mL collected during the entire study period for immune response assessments.

### 5.6.11. Study vaccines administration

- After completing all prerequisite procedures prior to vaccination, 1 dose of study vaccine(s) will be administered IM in the deltoid (refer to Section 6.3 for detailed description of the administration procedure). If the investigator or delegate determines that the subject's health on the day of administration temporarily precludes vaccine(s) administration, the visit will be rescheduled within the allowed interval for this visit (refer to Table 5).
- The subjects will be observed closely for at least 30 minutes following the administration of the vaccine(s), with appropriate medical treatment readily available in case of anaphylaxis.

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

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

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

### 5.6.13. Recording of adverse events, serious adverse events, pregnancies, and adverse events of special interest

- Refer to Section 8.3 for procedures for the investigator to record adverse events (AEs), medically attended AEs, SAEs, pregnancies, and AESIs. Refer to Section 8.4 for guidelines and how to report SAE, pregnancy, and AESI reports to PPD.

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

#### 5.6.13.1. Subject diary

A pDiary hereafter referred to as Subject Diary will be used in this study to capture solicited AEs. 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 AEs 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 Diary. 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 AEs and body temperature.

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

The subject/subject's parent(s)/LAR(s) should be instructed how to perform body temperature (preferably axilla) measurement using the thermometer provided by the site, and to record the body temperature in the evening. If the subject feels unusually hot or cold during the day, the subject or parent(s)/LAR(s) should check the body temperature. If the subject has a fever, the highest body temperature observed that day should be recorded in the Subject Diary.

#### 5.6.13.2. 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.

##### *5.6.13.2.1. Subject diary reminder calls*

Subject Diary reminder calls will be performed at 3 and 5 days ***(±1 day)*** after each vaccination ***(i.e., Day 4 and Day 6 after the first vaccination and accordingly after the second vaccination)***. ***(Amended 29 Aug 2018)*** The purpose of this call is to remind the subject/subject's parent(s)/LAR(s) about completion of the Subject Diary. The call follows the Subject Diary Reminder Telephone Call Script provided to the site. The

subject/subject's parent(s)/LAR(s) should be reminded to contact the site via the telephone number provided in the informed consent to discuss medical questions.

#### 5.6.13.3. Safety follow-up calls

Safety follow-up calls will be performed on Day 15 and Day 75. Please see Table 5 for the intervals allowed between study visits.

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 AE (including SAEs, AESIs, medically attended AEs, and/or AEs leading to withdrawal) and concomitant medications or vaccinations associated with those events. All safety information described by the subject must be written down in a designated location within the source document and not written on the script used for the telephone call.

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

The subject/subject's parent(s)/LAR(s) will be instructed to contact the site as soon as possible to report potential unsolicited AEs that required hospitalization, emergency room visit, or visit to/by a health care provider that were of concern. The detailed information about the reported unsolicited AEs will be collected by qualified site personnel during the interview and will be documented in the subject's records.

### 5.6.14. 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 Biospecimen Management section of the SPM and the central laboratory manual for detailed instructions for the collection, handling, processing, storage, and shipment of the samples.

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 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 Amendment 2 Investigator Agreement, where it is noted that the investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

If additional testing is performed, the marker priority ranking given in Section 5.7.4 may be changed.

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' selected 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 10.5.5 for the definition of analysis sets to be analyzed). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals' selected 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.

### 5.7.2. Biological samples

The collection of blood samples during the study are defined in Table 6.

**Table 6 Biological samples**

| Sample type | Quantity (per sample) | Unit | Study group | Time points |
|---|---|---|---|---|
| Blood | 20 | mL | MenABCWY | Visit 1 (Day 1)<br>Visit 2 (Day 31)<br>Visit 4 (Day 91) |
| Blood | 20 | mL | rMenBOMV+ACWY_S[1] | Visit 1 (Day 1)<br>Visit 2 (Day 31)<br>Visit 4 (Day 91) |
| Blood | 20 | mL | rMenBOMV+ACWY_D[2] | Visit 1 (Day 1)<br>Visit 2 (Day 31)<br>Visit 4 (Day 91) |
| Blood | 20 | mL | rMenBOMV | Visit 1 (Day 1)<br>Visit 2 (Day 31)<br>Visit 4 (Day 91) |
| Blood | 20 | mL | MenACWY | Visit 1 (Day 1)<br>Visit 2 (Day 31) |

[1]S refers to administration in the same arm (approximately 2.5 cm apart).
[2]D refers to administration in 2 different arms.

### 5.7.3. Laboratory assays

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 the GSK or designated laboratory in a blinded manner towards the treatment arm and to the study visit.

**Table 7 Humoral immunity (antibody determination)**

| System | Component | Method | Kit/ Manufacturer | Unit[1] | Cut-off[1] | Laboratory[2] |
|---|---|---|---|---|---|---|
| Humoral | *Neisseria meningitidis* Serogroup B M14459 (fHbp) | hSBA | In-house | 1/Dilution | LLOQ | GSK Biologicals or a laboratory designated by GSK Biologicals[3] |
| | *Neisseria meningitidis* Serogroup B 96217 (NadA) | | | 1/Dilution | LLOQ | |
| | *Neisseria meningitidis* Serogroup B NZ98/254 (PorA P1.4) | | | 1/Dilution | LLOQ | |
| | *Neisseria meningitidis* Serogroup B M07-0241084 (NHBA) | | | 1/Dilution | LLOQ | |
| | *Neisseria meningitidis* Serogroup A | | | 1/Dilution | LLOQ | |
| | *Neisseria meningitidis* Serogroup C | | | 1/Dilution | LLOQ | |
| | *Neisseria meningitidis* Serogroup W-135 | | | 1/Dilution | LLOQ | |
| | *Neisseria meningitidis* Serogroup Y | | | 1/Dilution | LLOQ | |

[1]Assay cut-offs and units will be determined following the completion of the qualification of hSBA for each of the 8 serogroups. In case testing is performed at another GSK designated laboratory, the assay cut-offs may also need to be adapted accordingly. Any of these changes will be documented in a protocol amendment or in the clinical study report.
[2]Refer to Appendix B for the possible laboratory addresses.
[3]GSK Biologicals laboratory refers to the Clinical Laboratory Sciences in Rixensart, Belgium; Wavre, Belgium; Marburg, Germany.
GSK = GlaxoSmithKline; hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation

Additional exploratory testing on the vaccine(s) 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 8 Immunological read-outs**

| Blood sampling time point | | No. subjects[1] | Component | Components priority rank[2] |
|---|---|---|---|---|
| Type of contact and time point | Sampling time point | | | |
| Visit 1 (Day 1) | Pre-Vacc 1 | 500 | Serogroup B M14459<br>Serogroup B M07-0241084<br>Serogroup B 96217<br>Serogroup B NZ98/254<br>Serogroup C<br>Serogroup Y<br>Serogroup W-135<br>Serogroup A | 1<br>2<br>3<br>4<br>5<br>6<br>7<br>8 |
| Visit 2 (Day 31) | Post-Vacc 1 1 | 500 | Serogroup B M14459<br>Serogroup B M07-0241084<br>Serogroup B 96217<br>Serogroup B NZ98/254<br>Serogroup C<br>Serogroup Y<br>Serogroup W-135<br>Serogroup A | 1<br>2<br>3<br>4<br>5<br>6<br>7<br>8 |
| Visit 4 (Day 91)[3] | Post-Vacc 2 | 400 | Serogroup B M14459<br>Serogroup B M07-0241084<br>Serogroup B 96217<br>Serogroup B NZ98/254<br>Serogroup C<br>Serogroup Y<br>Serogroup W-135<br>Serogroup A | 1<br>2<br>3<br>4<br>5<br>6<br>7<br>8 |

[1]Approximate number of subjects.
[2]Priority ranking for the serum bactericidal assay using human complement (hSBA) testing using the 8 indicator strains may be subject to change following the selection of the most appropriate hSBA format for each of the 8 serogroups. This will be documented in a protocol amendment or the clinical study report.
[3]No blood collection and assays will be performed at this time point for the MenACWY treatment group.
Pre-Vacc: pre-vaccination; Post-Vacc: post-vaccination

In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analyzed according to priority ranking provided in Table 8.

## 5.7.5. Immunological correlates of protection

No generally accepted immunological correlate of protection has been demonstrated so far against *N. meningitidis* serogroups A, B, W-135, and Y.

An hSBA titer ≥4 is a generally accepted correlate of protection against invasive meningococcal disease caused by *N. meningitidis* serogroup C.

Assessment of the protection level will be performed 1 month after the last vaccination for the primary objective.

The immunological assay results will be communicated to the investigator as soon as they become available and in any case no later than 12 months after the visit date at which sampling allows the assessment of protection.

The investigator is encouraged to share the immunological assay results for non-responders with the study subjects/subjects' parent(s)/LAR(s).

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.

# 6. STUDY VACCINES ADMINISTRATION

## 6.1. Description of study vaccines

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

The formulations of the study vaccines are shown in Table 9.

## Table 9 Study vaccines

| Treatment name | Vaccine name | Formulation | Presentation | Volume to be administered | Number of doses |
|---|---|---|---|---|---|
| MenABCWY | MenACWY lyo | MenA=10µg,CRM197=16.7-33.3µg; MenC=5µg,CRM197=7.1-12.5µg; MenW=5µg,CRM197=3.3-8.3µg; MenY=5µg,CRM197=5.6-10µg; $NaH_2PO_4$=0.328mg; Sucrose=12.5mg | Lyophilized component in a vial | 0.5 mL | 2 |
| | rMenB+OMV NZ | rp936-741=50µg; rp287-953=50µg; rp961c=50µg; OMV NZ98/254=25µg; $Al(OH)_3$=1.5mg; Histidine=776µg; NaCl=3.125mg; Sucrose=10mg; Water=0.5mL | Suspension for injection in a pre-filled syringe | | |
| rMenB+OMV NZ | rMenB+OMV NZ | rp936-741=50µg; rp287-953=50µg; rp961c=50µg; OMV NZ98/254=25µg; $Al(OH)_3$=1.5mg; Histidine=776µg; NaCl=3.125mg; Sucrose=10mg; Water=0.5mL | Suspension for injection in a pre-filled syringe | 0.5 mL | 2 |
| MenACWY | MenA lyo | MenA=10µg,CRM197=16.7-33.3µg; $KH_2PO_4$=5mM; Sucrose=12.5mg | Lyophilized component in a vial | 0.5 mL | 1 or 2 |
| | MenCWY liquid | MenC=5µg,CRM197=7.1-12.5µg; MenW=5µg,CRM197=3.3-8.3µg; MenY=5µg,CRM197=5.6-10µg; NaCl=4.5mg; $Na_3PO_4$=10mM; $NaH_2PO_4$=2.5mM; $Na_2HPO_4$=7.5mM; Water=0.5mL | Liquid component in a vial | | |

Note: MenACWY is approved in adults as a single dose injection. In this study, for study groups rMenBOMV+ACWY_S and rMenBOMV+ACWY_D, 2 injections of MenACWY will be administered.

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

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

## 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 label storage condition) impacting the study vaccines must be reported in the appropriate (electronic) temperature excursion decision form (Advanced Temperature Excursion Analysis and Management [ATEAM]). The impacted study vaccines must not be used and must be stored in quarantine at label temperature conditions until usage approval has been obtained from GSK Biologicals/PPD.

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

The dosage and administration of the study vaccines are presented in Table 10.

In addition to the Investigator Brochure for MenABCWY and SmPCs for the commercial MenACWY and rMenB+OMV NZ vaccines, please also refer to the Critical Expert Overview document, which addresses the off-label administration of the MenACWY and rMenB+OMV NZ vaccines in this study.

## Table 10 Dosage and administration

| Type of contact and time point | Study group | Treatment name | Volume to be administered | Route[1] | Site | | |
|---|---|---|---|---|---|---|---|
| | | | | | Location | Directionality[2] | Laterality[3] |
| Visit 1 (Day 1) | MenABCWY | MenABCWY[4] | 0.5 mL | IM | Deltoid | Upper or lower | Non-dominant |
| | rMenBOMV+ACWY_S[5] | rMenB+OMV NZ | 0.5 mL | | Upper Deltoid (approximately 2.5 cm above MenACWY injection) | Upper | Non-dominant |
| | | MenACWY[6] | 0.5 mL | | Lower Deltoid (approximately 2.5 cm below rMenB+OMV NZ injection) | Lower | Non-dominant |
| | rMenBOMV+ACWY_D[7] | rMenB+OMV NZ | 0.5 mL | | Deltoid | Upper or lower | Non-dominant |
| | | MenACWY[6] | 0.5 mL | | Deltoid | Upper or lower | Dominant |
| | rMenBOMV | rMenB+OMV NZ | 0.5 mL | | Deltoid | Upper or lower | Non-dominant |
| | MenACWY | MenACWY[6] | 0.5 mL | | Deltoid | Upper or lower | Non-dominant |
| Visit 3 (Day 61) | MenABCWY | MenABCWY[4] | 0.5 mL | IM | Deltoid | Upper or lower | Non-dominant |
| | rMenBOMV+ACWY_S[5] | rMenB+OMV NZ | 0.5 mL | | Upper Deltoid (approximately 2.5 cm above MenACWY injection) | Upper | Non-dominant |
| | | MenACWY[6] | 0.5 mL | | Lower Deltoid (approximately 2.5 cm below rMenB+OMV NZ injection) | Lower | Non-dominant |
| | rMenBOMV+ACWY_D[7] | rMenB+OMV NZ | 0.5 mL | | Deltoid | Upper or lower | Non-dominant |
| | | MenACWY[6] | 0.5 mL | | Deltoid | Upper or lower | Dominant |
| | rMenBOMV | rMenB+OMV NZ | 0.5 mL | | Deltoid | Upper or lower | Non-dominant |

[1]Intramuscular (IM)
[2]Directionality is a qualifier for further detailing the location of the vaccine(s) administration (e.g. Upper, Lower)
[3]The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the vaccine(s) in the non-dominant arm, an injection in the dominant arm may be performed.
[4]MenABCWY is to be reconstituted as a 0.5 mL solution between MenACWY lyo (lyophilized component) and rMenB+OMV NZ (liquid component) by trained staff.
[5]S refers to administration in the same arm (approximately 2.5 cm apart).
[6]MenACWY is to be reconstituted as a 0.5 mL solution between Men A lyo (lyophilized component) and Men CWY liquid (liquid component) by trained staff.
[7]D refers to administration in 2 different arms.

## 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 10% additional vaccine doses will be supplied to replace those that are unusable.

## 6.5. Contraindications to subsequent vaccination

The following events constitute absolute contraindications to further administration of MenABCWY, rMenB+OMV NZ, or MenACWY. If any of these events occur during the study, the subject must not receive additional doses of vaccine(s) but may continue other study procedures at the discretion of the investigator (see Section 8.5).

- Anaphylaxis following the administration of vaccine(s).
- Pregnancy (see Section 8.2.1).
- Any occurrence of an event listed in the exclusion criteria, which must always be re-assessed by the investigator before administration of the second dose of study vaccine(s). Refer to Section 4.3.
- Subjects who experience any SAE judged to be possibly or probably related to study vaccine(s), including hypersensitivity reactions.
- Subjects who develop any new condition which, in the opinion of the investigator, may pose additional risk to the subject if he/she continues to participate in the study.
- Any condition that in the judgment of the investigator would make IM injection unsafe.

The following events constitute contraindications to administration of MenABCWY, rMenB+OMV NZ, or MenACWY 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 Section 5.5).

- Body temperature elevation (i.e. fever) within 3 days prior to intended study vaccination. Fever is defined as temperature ≥38.0°C.
- Significant acute illness (e.g. acute severe febrile illness) within 7 days prior to vaccination.
- Administration of any other vaccine 14 days (for inactivated vaccines), 28 days (for live vaccines), or 7 days (for influenza vaccines) prior to vaccination.

Additionally, the following event warrants the delay of blood sample collection for immunogenicity assessments in this study.

- Receipt of systemic antibiotics with the previous 3 days before blood sample collection.

In the event that a subject meets the criterion for delay of blood sample collection, blood sample collection may proceed once the appropriate window for delay has passed.

## 6.6. Warnings and precautions

Please also refer to the Investigator Brochure for MenABCWY. Please refer to the approved SmPCs for the commercial MenACWY and rMenB+OMV NZ vaccines.

## 6.7. Concomitant medications/products and concomitant vaccinations

At each study 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 medications/products and concomitant vaccines must be recorded in the subject records and the eCRF.

- All concomitant medications/products, except vitamins and dietary supplements, administered through 30 days post-vaccination.
- Any concomitant vaccination administered in the period starting 28 days before the first dose of study vaccine(s) and ending at the last study visit (Day -28 to Day 91).
- Prophylactic medication (i.e. medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).

  For example, an antipyretic 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 temperature ≥38.0°C regardless the location of measurement). The preferred location for measuring temperature in this study is the axilla.
- Any concomitant medications/products/vaccines listed in Section 6.7.2.
- Any concomitant medications/products administered for treatment of an AE to be recorded as per protocol-specified reporting period (see Table 11).
- Any concomitant medications/products/vaccines relevant to an SAE/AESI to be reported as per protocol or administered at any time during the study period for the treatment of an SAE/AESI. In addition, concomitant medications relevant to SAEs and AESIs need to be recorded on the Expedited Adverse Events Report.
- The use of antipyretic and/or other medications to prevent (prophylactic use) and/or treat fever during the first 7 days after vaccination to be recorded in the eCRF as well.

### 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 10.5 for analyses sets to be analyzed.

- Any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) used during the study period.
- Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 consecutive days in total) during the study period. Inhaled and topical steroids are allowed.
- Long-acting immune-modifying drugs administered at any time during the study period (e.g. infliximab).
- A vaccine not foreseen by the study protocol administered during the period of 14 days (for inactivated vaccines), 28 days (for live vaccines), or 7 days (for influenza vaccines) before or after administration of the study vaccine(s) at Visit 1 and Visit 3*.

  *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 SmPC and according to local governmental recommendations and provided a written approval of the sponsor is obtained.
- Drug and/or alcohol abuse that, in the opinion of the investigator, will interfere with the results of the study or pose additional risk to the subject.

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

At each study visit/safety call subsequent to the first vaccination/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 subject records and the eCRF.

Subjects may be eliminated from the per-protocol cohort for immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response (i.e. human immunodeficiency virus or hematological malignancies) or are confirmed to have an alteration of their initial immune status.

For analysis purposes, intercurrent conditions will be identified using AEs reported in the eCRFs during the study.

## 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 AE or 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 unfavorable 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(s) or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with study vaccine(s) administration.
- 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).

Adverse events 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 first study vaccination. These events will be recorded in the medical history section of the eCRF.

### 8.1.2. Definition of a serious adverse event

An 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, diarrhea, 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 AEs") occurring in the hours and days following a vaccination, to be collected by the subjects/parent(s)/LAR(s) for 7 consecutive days, using a pre-defined Subject Diary.

The following solicited AEs are included in the Subject Diary.

#### 8.1.3.1. Solicited local adverse events

Solicited local (injection site) AEs for this study are pain, erythema, swelling, and induration. The preferred location for measuring temperature in this study is the axilla. Solicited local AEs will be recorded and collected according to which vaccine was administered and the site of administration (e.g. upper or lower deltoid and the arm used for administration).

#### 8.1.3.2. Solicited systemic adverse events

Solicited systemic AEs for this study are fever (body temperature ≥38.0°C), nausea, myalgia, arthralgia, headache, and fatigue.

#### 8.1.3.3. Other solicited adverse events

The use of analgesics/antipyretics (preferably paracetamol) for either prophylactic or treatment purposes will also be recorded as other solicited events in the Subject Diary and verified onto specific eCRFs and subject medical records.

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

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

- Solicited local or systemic AE that continues beyond day 7 after vaccination.
- Solicited local or systemic AE that leads to a visit to a healthcare provider (medically attended AE, see Section 8.3.3.4).
- Solicited local or systemic AE leading to the subject withdrawing from the study or the subject being withdrawn from the study by the investigator (AE leading to withdrawal).
- Solicited local or systemic AE that otherwise meets the definition of an SAE (see Section 8.1.2).

### 8.1.4. Unsolicited adverse events

An unsolicited AE is an AE that was not solicited using a Subject Diary and that was spontaneously communicated by a subjects/parent(s)/LAR(s) who has signed the informed consent or a solicited local or systemic AE that continues beyond the solicited period at day 7 after vaccination.

Unsolicited AEs will be collected during interview with the subjects/parent(s)/LAR(s) and by review of available medical records at the next visit. Unsolicited AEs will be reviewed at the safety follow-up calls as well.

Subjects/parent(s)/LAR(s) will be instructed to contact the site as soon as possible to report potential unsolicited AEs that required hospitalization, emergency room visit, or

visit to/by a health care provider that were of concern to the subjects/parent(s)/LAR(s). The detailed information about the reported unsolicited AEs will be collected by qualified site personnel during the interview and will be documented in the subject's records. Unsolicited AEs (including those of concern to subjects/parent(s)/LAR(s) and those which led to a medical visit but were not of concern) will be collected during the visit interview.

Unsolicited AEs that are not medically attended nor perceived as a concern by subjects/parent(s)/LAR(s) will be collected during interview with the subjects/parent(s)/LAR(s) 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

Only immunogenicity blood samples will be collected in this study (i.e. no routine clinical laboratory assessments will be performed per protocol). Should any local laboratory tests be performed during the study for a subject, AEs will be recorded as follows.

In absence of diagnosis, abnormal laboratory findings (e.g. clinical chemistry, hematology, urinalysis) or other abnormal assessments that are judged by the investigator to be clinically significant will be recorded as an AE or SAE if they meet the definition of an AE or SAE (refer to Sections 8.1.1 and 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 associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or 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.

### 8.1.6. Adverse events of special interest

Adverse events of special interest are predefined (serious or non-serious) AEs of scientific and medical concern specific to the product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate, because such an event might warrant further investigation in order to characterize and understand it.

Arthritis is the only AESI in this study as described in Section 1.3.1 and Section 8.1.6.1.

#### 8.1.6.1. Arthritis

Cases of arthritis are defined according to the following ad-hoc definition:

- Presence of physical examination findings of swelling, redness, heat, or limitation in range of motion

  and/or

- Presence of diagnostic imaging studies interpreted by a health care provider as demonstrating evidence of joint inflammation and/or arthrocentesis results evidencing inflammation

Due to the heterogeneity of the presentation of arthritis, which can be either acute or chronic, the threshold of duration of 6 weeks is to be considered.

The list of preferred terms corresponding to the diagnosis of arthritis are those included in the Medical Dictionary for Regulatory Activities (MedDRA) Standardized MedDRA Queries Narrow "Arthritis." For any new diagnosis of arthritis (serious or non-serious) in a study subject, the investigator (or designate) must complete an electronic Expedited Adverse Events Report and an ad-hoc eCRF page on arthritis to further characterize this AESI.

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

### 8.2.1. Pregnancy

Female subjects who are pregnant or lactating at the time of vaccination must not receive additional doses of study vaccine(s) but may continue other study procedures 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 an SAE.

Note: The pregnancy itself should always be recorded on a paper pregnancy report.

The following should always be considered as SAEs and will be reported as described in Sections 8.4.1 and 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 fetus after 22 weeks of gestation).

  Note: the 22 weeks cut-off in gestational age is based on the World Health Organization-International Classification of Diseases 10 noted in the European Medicines Agency 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 fetus 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 vaccine(s) will be reported to PPD 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

The time period for collecting and recording AEs will begin at the time of informed consent signature and through study discharge.

All AEs starting within 30 days following administration of each dose of study vaccine(s) must be recorded into the subject records and 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 will begin at the time of informed consent signature and will end 30 days following administration of the last dose of study vaccine(s) for each subject. See Section 8.4 for instructions on reporting of SAEs.

All medically attended AEs will be collected and recorded from the time of informed consent signature.

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of informed consent signature.

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 time of informed consent signature and will end 30 days following administration of the last dose of study vaccine(s). See Section 8.4 for instructions on reporting of pregnancies.

The time period for collecting and recording of AESIs will begin at the time of informed consent signature and will end 30 days following administration of the last dose of study vaccine(s). See Section 8.4 for instructions on reporting of AESIs.

An overview of the protocol-required reporting periods for AEs, SAEs, and pregnancies is given in Table 11.

**Table 11 Reporting periods for collecting safety information**

| Event | Visit 1 | | Safety Call 1 | Visit 2 | Visit 3 | | Safety Call 2 | Visit 4 Study Conclusion |
|---|---|---|---|---|---|---|---|---|
| | Day 1 | Day 7 | Day 15 | Day 31 | Day 61 | Day 67 | Day 75 | Day 91 |
| Solicited local and systemic AEs[1,2] | ■ | ■ | | | ■ | ■ | | |
| Unsolicited AEs[1,2,3] | ■ | ■ | ■ | | ■ | ■ | ■ | ■ |
| Medically attended AEs[1,3] | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ |
| AESI[3] | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ |
| AEs/SAEs leading to withdrawal from the study[1,3] | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ |
| SAEs[1,3] | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ |
| SAEs related to study participation or concurrent GSK medication/vaccine[3] | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ |
| Pregnancies[3] | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ |

[1]All concomitant medications/products, except vitamins and dietary supplements, administered during the entire study period (Day 1 to Day 91), and used to treat an AE or a SAE, should be recorded in the electronic case report form and subject medical records.
[2]Safety information will not be collected at the Visit 3 time point for the MenACWY group administered only 1 dose of vaccine at Visit 1 (no Visit 3 performed).
[3]All AEs/SAEs, including those related to study participation or to a concurrent GSK medication/vaccine should be recorded starting from informed consent form signature, if a separate visit occurs before Visit 1 (maximum 5 days before Visit 1).
AE = adverse event; AESI = adverse event of special interest; GSK = GlaxoSmithKline; 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 11. 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 vaccine(s), 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(s) or since the previous visit?"*

OR

"*Has your child acted differently or felt different in any way since receiving the vaccine(s) or since the last visit?"*

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 PPD instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by PPD. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to PPD.

The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

#### 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 in Table 12.

**Table 12 Intensity scales for solicited symptoms**

| Adverse Event | Intensity grade | Parameter |
|---|---|---|
| Pain at injection site | 0 | None |
| | 1 | Mild: Any pain neither interfering with nor preventing normal every day activities |
| | 2 | Moderate: Painful when limb is moved and interferes with every day activities |
| | 3 | Severe: Significant pain at rest. Prevents normal every day activities |
| Erythema at injection site<br>Swelling at injection site<br>Induration at injection site | 0 | Grade 0: <25 mm surface diameter |
| | 1 | Grade 1: 25-50 mm surface diameter |
| | 2 | Grade 2: 51-100 mm surface diameter |
| | 3 | Grade 3: >100 mm surface diameter |
| Fever[1] | | Record temperature in °C |
| Nausea | 0 | None |
| | 1 | Mild: Nausea present but not interfering with oral intake |
| | 2 | Moderate: Nausea leading to decreased oral intake |
| | 3 | Severe: Nausea leading to minimal to no oral intake |
| Myalgia | 0 | None |
| | 1 | Mild: Myalgia present but does not interfere with activity |
| | 2 | Moderate: Myalgia that interferes with normal activity |
| | 3 | Severe: Myalgia that prevents normal activity |
| Arthralgia | 0 | None |
| | 1 | Mild: Arthralgia present but does not interfere with activity |
| | 2 | Moderate: Arthralgia that interferes with normal activity |
| | 3 | Severe: Arthralgia that prevents normal activity |
| Headache | 0 | None |
| | 1 | Mild: Headache present but does not interfere with activity |
| | 2 | Moderate: Headache that interferes with normal activity |
| | 3 | Severe: Headache that prevents normal activity |
| Fatigue | 0 | None |
| | 1 | Mild: Fatigue that does not interfere with activity |
| | 2 | Moderate: Fatigue that causes some interference with activity |
| | 3 | Severe: Fatigue that prevents daily activity |

[1]The preferred route for measuring and recording temperature in this study is the axilla. When there is no other alternative, the temperature may be recorded by another route. If the temperature is taken by another route (oral, rectal, or tympanic), the route should be documented. Fever is defined as a body temperature ≥38°C.
Note: Temperature will be recorded in the evening. If additional temperature measurements are to be performed at other times of the day, the highest temperature measured will be recorded in the eCRF.

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.

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

The severity of events reported on the Adverse Events 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 vaccine(s) 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) 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 vaccine(s) will be considered and investigated. The investigator will also consult the Investigator Brochure and/or SmPC 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 PPD. 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 PPD. 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 AEs 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(s) contributed to the AE. |
| NO: | There is no reasonable possibility that the AE is causally related to the administration of the study vaccine(s). There are other, more likely causes and administration of the study vaccine(s) 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(s), 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 or 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 and source documents.

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

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

Serious AEs that occur in the time period defined in Section 8.3 will be reported promptly to PPD within the timeframes described in Table 13, 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 PPD within the timeframes described in Table 13, once the investigator becomes aware of the pregnancy.

Adverse events of special interest that occur in the time period defined in Section 8.3 will be reported promptly to PPD within the timeframes described in Table 13, once the investigator determines that the event meets the protocol definition of an AESI.

**Table 13 Timeframes for submitting serious adverse event, pregnancy, and other events reports**

| 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* | paper pregnancy notification report | 2 weeks* | paper pregnancy follow-up report |
| AESIs | 24 hours**‡ | electronic Expedited Adverse Events Report | 24 hours* | electronic Expedited Adverse Events Report |

* Timeframe allowed after receipt or awareness of the information.
**Timeframe allowed once the investigator determines that the event meets the protocol definition of a AESI.
‡ The investigator will be required to confirm review of the SAE/AESI causality by ticking the "reviewed" box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE/AESI.
AESI = adverse event of special interest; SAE = serious adverse event

### 8.4.2. Contact information for reporting serious adverse events, pregnancies, and adverse events of special interest

| Study Contact for Reporting SAEs, AESIs, and pregnancies |
|---|
| Refer to the local study contact information document. |
| **Back-up Study Contact for Reporting SAEs, AESIs, and pregnancies** |
| 24/24 hour and 7/7 day availability:<br><br>**PPD Pharmacovigilance**<br>EMEA SAE Hotline: PPD<br>EMEA SAE fax: PPD<br>Email address: PPD |

### 8.4.3. Completion and transmission of SAE reports

Once an investigator becomes aware that an 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 an 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 PPD Pharmacovigilance (at PPD ) 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

Once the investigator becomes aware that a subject is pregnant, the investigator (or designate) must complete the required information onto the paper pregnancy report WITHIN 2 WEEKS. The investigator (or designate) must complete and fax a pregnancy notification form to PPD Pharmacovigilance (at PPD ) after entering or updating information within the ***paper*** pregnancy ***report***. ***(Amended 29 Aug 2018)***

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

### 8.4.5. Reporting of adverse events of special interest

Once an AESI is diagnosed (serious or non-serious) in a study subject, the investigator (or designate) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS after he/she becomes aware of the diagnosis. The report allows to specify that the event is an AESI and whether it is serious or non-serious. 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 an AESI, 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 AESI causality by ticking the “reviewed” box in the electronic Expedited Adverse Events Report within 72 hours of submission of the AESI.

Refer to Section 8.4.3.1 for back-up system in case the electronic reporting system does not work.

#### 8.4.6. Updating of serious adverse event, pregnancy, and adverse events of special interest information after removal of write access to the subject's electronic case report form

When additional SAE, pregnancy, or AESI 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 Study Contact Information in Section 8.4.2) within the designated reporting time frames specified in Table 13.

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

The investigator will promptly report all SAEs to PPD in accordance with the procedures detailed in Section 8.4.1. PPD 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 PPD policy and are forwarded to investigators as necessary. An investigator safety report is prepared for an SAE(s) that is both attributable to the study vaccine(s) 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 PPD (within 24 hours for SAEs; refer to Table 13).

All SAEs and AESIs (serious or non-serious) 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, AESIs (serious or non-serious), 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 PPD using an electronic Expedited Adverse Events Report and/or pregnancy report as applicable.

PPD 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, PPD 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 PPD using the paper pregnancy report and the Expedited Adverse Events Report if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs for this study, if the pregnancy outcome is an SAE, it should always be reported as an 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 SAEs/AESIs should be recorded in Expedited Adverse Events Report of the subject's eCRF (refer to Section 6.7).

## 8.7. Subject card

Study subjects/subjects' parent(s)/LAR(s) 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' parent(s)/LAR(s) 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 returns for the concluding visit foreseen in the protocol is considered to have completed the study.

## 9.2. Subject withdrawal

Subjects withdrawn from the study will not be replaced.

### 9.2.1. Subject withdrawal from the study

From an analysis perspective, a "withdrawal" from the study refers to when a subject does not come back for the concluding visit 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 "withdrawn" 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 to contact those subjects who do not return for scheduled visits or follow-up. At a minimum, the investigator will contact the subject or subject's parent(s)/LAR(s) via 3 telephone calls and a certified letter to the last known address.

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 AE
- Unsolicited non-serious AE
- Solicited AE
- Protocol violation (specify)
- Consent withdrawal, not due to an AE*
- 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 an SAE/AE until resolution of the event (see Section 8.5.1.2).

### 9.2.2. Subject withdrawal from study vaccines

A "withdrawal" from the study vaccine(s) refers to when a subject does not receive the complete treatment, i.e. when no further planned dose is administered from the date of withdrawal. A subject withdrawn from the study vaccine(s) may not necessarily be withdrawn from the study as further study procedures or follow-up may be performed (safety or immunogenicity) if planned in the study protocol.

Information relative to premature discontinuation of the study vaccine(s) will be documented on the Vaccine Administration page/screen of the eCRF. The investigator will document whether the decision to discontinue further vaccination/treatment 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 AE
- Unsolicited non-serious AE
- Solicited AE
- Not willing to be vaccinated
- Other (specify)

## 9.3. Screen failures

Screen failures are subjects who withdraw or are withdrawn from the study following informed consent, but before randomization to study treatment. Information relative to screen failures will be documented on the Screening Conclusion page/screen of the eCRF. The investigator will document whether the screen failure decision 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 the screen failure:

- Consent withdrawal, not due to an SAE
- Eligibility criteria not fulfilled (inclusion and exclusion criteria)
- Lost to follow-up
- Migrated or moved from the study area
- Other (specify)
- Protocol violation

- SAE not related to study participation or to a GSK concurrent medication
- SAE related to study participation or to a GSK concurrent medication

# 10. STATISTICAL METHODS

## 10.1. Primary endpoint

- Immune responses against *N. meningitidis* serogroup B* test strains and *N. meningitidis* serogroups A, C, W-135, and Y, as measured by hSBA, 1 month after the last vaccination in all study groups

  – hSBA GMTs against each of the *N. meningitidis* serogroup B test strains and against *N. meningitidis* serogroups A, C, W-135, and Y

  – hSBA GMTs against all of *N. meningitidis* serogroup B test strains (pooled)

  – Percentage of subjects with hSBA titers ≥ the lower limit of quantitation (LLOQ) against each of the *N. meningitidis* serogroup B test strains and against *N. meningitidis* serogroups A, C, W-135, and Y

  – Percentage of subjects with a 4-fold increase in hSBA titers against *N. meningitidis* serogroups B test strains and against *N. meningitidis* serogroups A, C, W-135, and Y

  – hSBA geometric mean ratios (GMRs) against each of the *N. meningitidis* serogroup B test strains and against *N. meningitidis* serogroups A, C, W-135, and Y at 1 month after the last vaccination against baseline (Day 1)

*Serogroup B strains that will be tested are M14459 (factor H binding protein; fHbp), 96217 (Neisserial adhesin A; NadA), NZ98/254 (PorA), and M07-0241084 (Neisseria heparin binding antigen; NHBA) and will be pooled to estimate the effect of immune interference due to stress to lymph nodes.

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 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 4 times the LLOQ; and c) for individuals whose pre-vaccination titers are ≥ the LLOQ, the post-vaccination titers must be at least 4 times the pre-vaccination titer.

The ratios of GMTs between study groups will be analyzed to evaluate effect of treatment as described below:

a. Immune interference due to stress to lymph nodes (lymph-node effect) in rMenBOMV+ACWY_S versus rMenBOMV+ACWY_D study groups, on the pooled B strains, and individually by serogroup A, C, W-135, Y, and B test strains.
b. Other unknown interference in the MenABCWY versus rMenBOMV+ACWY_S study groups, by serogroup A, C, W-135, Y, and B test strains.

c. The difference in immune response compared to control groups in rMenBOMV+ACWY_S versus rMenBOMV and MenACWY, rMenBOMV+ACWY_D versus rMenBOMV and MenACWY, and MenABCWY versus rMenBOMV and MenACWY study groups, by serogroup A, C, W-135, Y, and B test strains.

## 10.2. Secondary endpoints

Immunogenicity Endpoints

- Immune responses against *N. meningitidis* serogroup B* test strains and *N. meningitidis* serogroups A, C, W-135, and Y, as measured by hSBA, 1 month after the first vaccination in all groups (except for subjects in the MenACWY group)
  - hSBA GMTs against each of the *N. meningitidis* serogroup B test strains and against *N. meningitidis* serogroups A, C, W-135, and Y
  - hSBA GMTs against all of *N. meningitidis* serogroup B test strains (pooled)
  - Percentage of subjects with hSBA titers ≥ the LLOQ against each of the *N. meningitidis* serogroup B test strains and against *N. meningitidis* serogroups A, C, W-135, and Y
  - Percentage of subjects with a 4-fold increase in hSBA titers against *N. meningitidis* serogroups B test strains and against *N. meningitidis* serogroups A, C, W-135, and Y
  - hSBA GMRs against each of the *N. meningitidis* serogroup B test strains and against *N. meningitidis* serogroups A, C, W-135, and Y at 1 month after the first vaccination against baseline (Day 1)

*Serogroup B tests strains that will be tested are M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA), and M07-0241084 (NHBA).

Notes, as described in Section 10.1, also apply to the secondary endpoints.

The ratios of GMTs between study groups will be analyzed to evaluate effect of treatment as described below:

a. Immune interference due to stress to lymph nodes (lymph-node effect) in rMenBOMV+ACWY_S versus rMenBOMV+ACWY_D study groups, on the pooled B strains, and individually by serogroup A, C, W-135, Y, and B test strains.

b. Other unknown interference in MenABCWY versus rMenBOMV+ACWY_S study groups, by serogroup A, C, W-135, Y, and B test strains.

c. The difference in immune response compared to control groups in rMenBOMV+ACWY_S versus rMenBOMV, rMenBOMV+ACWY_D versus rMenBOMV, and MenABCWY versus rMenBOMV study groups, by serogroup B test strains.

Safety Endpoints

- Solicited local and systemic AEs in all study groups
  - Occurrence of solicited local and systemic AEs during the 7 days (including the day of vaccination) after each vaccination (Day 1 to Day 7 and Day 61 to Day 67 [Day 1 to Day 7 only for subjects in the MenACWY group])
- Unsolicited AEs in all study groups
  - Occurrence of unsolicited AEs during the 30 days (including the day of vaccination) after each vaccination (Day 1 to Day 31 and Day 61 to Day 91 [Day 1 to Day 31 only for subjects in the MenACWY group])
- SAEs, medically attended AEs, AEs leading to withdrawal, and AESIs, in all study groups from informed consent signature to Visit 4 (Day 91)

### *10.3. Tertiary endpoint*

***Endpoints related to the tertiary objective will be described in a separate statistical analysis plan. (Amended 29 Aug 2018)***

## 10.4. Determination of sample size

The sample size is for exploratory statistical analysis purposes only. There are no formal confirmatory hypotheses to be tested. The text in this section describes what can be observed with the current sample size.

Sample size calculation was performed using PASS 12 and SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

The potential immune interference due to immunological stress to lymph nodes is assumed to result in decreases to all of the 4 B test strains but to various extents. In a previous study (MenABCWY-011 [V102_15]), the GMT ratios ranged from 74% (-0.13 on $\log_{10}$ scale) to 50% (-0.3 $\log_{10}$ scale) with a mean of 64% (-0.19 on $\log_{10}$ scale). Because of this consistent decrease in GMT ratios in the MenABCWY group in comparison to the MenB group across the 4 serogroups, the presence of the lymph-node effect will be tested globally on all the serogroups together. A multivariate analysis of V102_15 data provided an estimate of $\sigma = 0.435$ (on $\log_{10}$ scale) for the standard deviation (SD) of the averaged GMTs across the 4 serogroups of the MenABCWY arm. That variability is higher than what would be expected by dividing the variance of a single serogroup by 4 due to the correlations existing between serogroups.

Therefore, assuming a SD of $\sigma = 0.435$ (in log form), group sample sizes of 100 in each study group will achieve a power of approximately 80% to reject the null hypothesis of equal means when the population mean difference is -0.130 (log GMT ratio 74%) with a SD of 0.435 for both groups and a significance level (alpha) of 10% using a 1-sided 2-sample equal-variance t-test. This calculation ignores the potential correlation that might exist between serogroups of the MenABCWY when pooled together.

The numerical results for the 2-sample t-test assuming equal variance (alternative hypothesis: $\delta < 0$) is shown in Table 14.

**Table 14 Sample size calculation results**

| Power | N1 | N2 | δ | σ | Alpha | Beta |
|---|---|---|---|---|---|---|
| 0.650 | 100 | 100 | -0.145 | 0.435 | 0.025 | 0.350 |
| 0.759 | 100 | 100 | -0.145 | 0.435 | 0.050 | 0.241 |
| 0.819 | 100 | 100 | -0.145 | 0.435 | 0.075 | 0.181 |
| 0.858 | 100 | 100 | -0.145 | 0.435 | 0.100 | 0.142 |
| 0.620 | 100 | 100 | -0.140 | 0.435 | 0.025 | 0.380 |
| 0.733 | 100 | 100 | -0.140 | 0.435 | 0.050 | 0.267 |
| 0.797 | 100 | 100 | -0.140 | 0.435 | 0.075 | 0.203 |
| 0.839 | 100 | 100 | -0.140 | 0.435 | 0.100 | 0.161 |
| 0.589 | 100 | 100 | -0.135 | 0.435 | 0.025 | 0.411 |
| 0.706 | 100 | 100 | -0.135 | 0.435 | 0.050 | 0.294 |
| 0.773 | 100 | 100 | -0.135 | 0.435 | 0.075 | 0.227 |
| 0.818 | 100 | 100 | -0.135 | 0.435 | 0.100 | 0.182 |
| 0.557 | 100 | 100 | -0.130 | 0.435 | 0.025 | 0.443 |
| 0.678 | 100 | 100 | -0.130 | 0.435 | 0.050 | 0.322 |
| 0.748 | 100 | 100 | -0.130 | 0.435 | 0.075 | 0.252 |
| **0.796** | **100** | **100** | **-0.130** | **0.435** | **0.100** | **0.204** |

The sample size calculation shows that with a power range of 80% to 90%, a global lymph-node effect is detectable when the GMT ratio is between 64% (approximately -0.19 on $\log_{10}$ scale) and 74% (-0.13) pooling 4 variants of B test strains together and using a 1-sided false-positive error rate of 10%.

A decrease in GMT ratios below 74% is acceptable as, for a lower mean ratio, the presence of a marginal lymph-node effect can be compensated with an increase in sample size in a formal non-inferiority study.

Assuming a rare event occurring at the rate of 1 out of 100, a sample size of 500 subjects in the study will have a probability of 99.3% to detect a rare AE.

A total of approximately 500 subjects (approximately 100 subjects in each group) are planned for enrollment into the study.

## 10.5. Analysis sets

### 10.5.1. All Enrolled Set

All subjects who signed an informed consent, underwent screening procedures, and have a subject number assigned.

### 10.5.2. All Exposed Set

All subjects in the All Enrolled Set who receive ***any*** study vaccination. ***(Amended 29 Aug 2018)***

### 10.5.3. Safety Set

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

All subjects in the All Exposed Set with any solicited AE data.

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

All subjects in the All Exposed Set who attended at least 1 visit or had at least 1 safety call or at least 1 follow-up event (such as withdrawal from the study) after receiving any study vaccination.

#### 10.5.3.3. 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[s] a subject received, rather than the vaccine[s] to which the subject may have been randomized).

### 10.5.4. Full Analysis Set, Immunogenicity

Each Full Analysis Set (FAS) will be defined by visit and by serogroup.

#### 10.5.4.1. Full Analysis Set 1

All subjects in the All Exposed Set who provided evaluable serum samples and whose assay results are available for at least 1 serogroup ***or B strain*** at Visit 4 for all study groups except the MenACWY group, or at Visit 2 for the MenACWY group. ***(Amended 29 Aug 2018)***

#### 10.5.4.2. Full Analysis Set 2

All subjects in the All Exposed Set who provided evaluable serum samples and whose assay results are available for at least 1 serogroup ***or B strain*** at Visit 2 for all study groups except the MenACWY group. ***(Amended 29 Aug 2018)***

#### 10.5.4.3. Full Analysis Set 3

All subjects in the All Exposed Set who provided evaluable serum samples and whose assay results are available for at least 1 serogroup ***or B strain*** at Visit 4 for all study groups except the MenACWY group, or at Visit 2 for the MenACWY group, and at baseline for all study groups. ***(Amended 29 Aug 2018)***

#### 10.5.4.4. Full Analysis Set 4

All subjects in the All Exposed Set who provided evaluable serum samples and whose assay results are available for at least 1 serogroup ***or B strain*** at Visit 2 and at baseline for all study groups except the MenACWY group. ***(Amended 29 Aug 2018)***

### 10.5.5. Per-Protocol Set, Immunogenicity

Per-Protocol Set (PPS) 1, PPS 2, PPS 3, and PPS 4 are the corresponding subsets of FAS 1, FAS 2, FAS 3, and FAS 4, respectively, who have no major protocol violations.

A major deviation is defined as a protocol deviation that is considered to have a significant impact on the immunogenicity result of the subject.

All protocol deviations will be identified prior to the analysis and a clinical judgment will be necessary to classify each deviation as "major" or not. These deviations and the judgment regarding their use will be listed and summarized in the final report.

A list of key major deviations is provided below, but not limited to:

- Subjects enrolled who did not meet entry criteria including age at enrollment
- Subjects incorrectly vaccinated
- Subjects who did not receive study vaccinations as planned in protocol
- Subjects who did not have blood draws as planned in protocol
- Subjects with a blood draw outside of allowed time window
- Subjects with a vaccination done outside of allowed time window

These key major deviations will be assessed based on the data collected in the eCRFs. The complete list of protocol deviations considered major for this study will be detailed in the statistical analysis plan and be reported in the final report.

### 10.5.6. Other analysis sets

No additional analysis sets are planned.

### 10.5.7. Subgroups

There are no intended subgroups for analysis.

## 10.6. Derived and transformed data

- Immunogenicity
  - The assay cut-off values will be defined by the laboratory before analysis and will be documented in a protocol amendment or in the clinical study report.
  - For the primary and secondary endpoints (see Section 10.1 and Section 10.2 , respectively), the percentage of subjects with hSBA titers ≥ LLOQ and with a

4-fold increase in hSBA titers against each of the *N. meningitidis* serogroup B test strains and against *N. meningitidis* serogroups A, C, W-135, and Y will be determined.

- The GMT 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.
- 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: for safety analyses, subjects who missed reporting symptoms (solicited/unsolicited) or concomitant medications will be analyzed further. The main safety analyses will contain missing data (missing safety values will not be imputed) but further analyses to assess the missing mechanism will be specified in the statistical analysis plan.
  - For the analysis of solicited symptoms, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the All Exposed Set will include only subjects/doses with documented safety data (i.e. symptom screen/sheet completed).
  - Solicited AEs will be assessed as described in Table 12 and Section 10.9.2.

## 10.7. Analysis of demographics

Demographic characteristics (age, gender, and ethnic origin) will be tabulated per study group for each analysis set as described in the statistical analysis plan.

The mean of continuous variables (plus range and SD) of the enrolled subjects, as a whole and per study group, will be calculated.

The distribution of discrete variables will be tabulated as a whole and per study group as described in the statistical analysis plan.

## 10.8. Analysis of immunogenicity

The primary and secondary immunogenicity analyses will be based on the PPS. If the difference between PPS and FAS is greater than 10%, a second analysis based on the FAS will be performed to complement the PPS analysis.

Titers below the LLOQ will be handled based on the assay procedure and will be described in the statistical analysis plan.

One of the main objectives of the study is to estimate the extent of a potential immune interference, due to immunological stress to lymph nodes in the arm where the combination vaccine is administered in comparison to injections in 2 different arms of individual vaccines. The sample size defines the conditions under which the observed

reduction in immune response will be attributed to a true lymph-node effect or is the consequence of natural variability. An acceptable probability of falsely detecting the lymph-node effect was set to 10% (1-sided test). The minimum probability of detecting the lymph node is set to 80%.

Criteria for the Statistical Test

rMenBOMV+ACWY_S will be declared statistically inferior if the 2-sided 80% confidence intervals (CIs) of the ratio of the GMT with rMenBOMV+ACWY_D as control is lower than 1. The lymph-node effect would therefore be the most probable cause for the decrease observed.

Analysis of hSBA GMT

An analysis of covariance (ANCOVA) model will be used to analyze post-vaccination log-transformed titers of hSBA for both the primary and secondary objectives (i.e. the hSBA at 1 month after the last vaccination and the hSBA at 1 month after the first vaccination, respectively). The ANCOVA model will be fitted to each serogroup/strain individually, and in addition the serogroup B strains will be grouped together to perform a pooled analysis. The GMTs obtained through the ANCOVA model will be called "adjusted" and the "unadjusted" GMTS will be obtained through descriptive statistics. Unadjusted and adjusted GMTs and associated 2-sided 80% CIs will be computed for each study group and for each strain at each visit. The fixed-effect model will include the age strata, treatment, serogroup, and center as fixed effects. The pre-vaccination log-transformed titer with centering at zero will be included as a continuous covariate. An interaction between serogroup and pre-vaccination log-transformed titer centered at zero will be included in the model. For each study group, adjusted GMTs and their 80% CIs will be obtained by exponentiating (base 10) the least squares means and the lower and upper limits of the 80% CIs of the log-transformed titers (base 10).

The following contrasts will be computed to investigate possible effects on the immune response based on strains common to each treatment group:

a. rMenBOMV+ACWY_S versus rMenBOMV+ACWY_D (test for immune interference, due to immunological stress to lymph node)
b. MenABCWY versus rMenBOMV+ACWY_S (test for other unknown immunological interference)
c. rMenBOMV+ACWY_S versus rMenBOMV
d. rMenBOMV+ACWY_S versus MenACWY
e. rMenBOMV+ACWY_D versus rMenBOMV
f. rMenBOMV+ACWY_D versus MenACWY
g. MenABCWY versus rMenBOMV
h. MenABCWY versus MenACWY

In addition, the distribution of antibody titers for each strain will be displayed using reverse cumulative distribution curves.

Analysis of Percentage of Subjects With Titers Above LLOQ and a 4-fold Increase

The percentage of subjects with titers above the LLOQ and a 4-fold increase as well as the associated 2-sided 80% Clopper-Pearson CIs will be computed by study group at each visit [Clopper, 1934]. In addition, differences in percentages and 2-sided 80% CIs between the groups will be calculated and the associated CI for the difference will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Unadjusted and adjusted GMTs and associated 2-sided 80% CIs will be computed for each group and for each strain at each visit. For each study group, adjusted GMTs and their 80% CIs will be obtained by exponentiating (base 10) the least square means and the lower and upper limits of the 80% CIs of the log-transformed titers (base 10).

The fixed-effect model for the individual serogroups/strains will include the age strata, treatment, and center as fixed effects. The fixed-effect model for the pooled analysis will include the age strata, treatment, strain, and center as fixed effects. The pre-vaccination log-transformed titer with centering at zero will be included as a continuous covariate. An interaction between serogroup and pre-vaccination log-transformed titer centered at zero will be included in the model.

Additionally, the group GMT ratios will be computed. The 2-sided 80% CIs for the group GMT ratio will be constructed by exponentiating the group difference of the least squares means of the log-transformed titers and the lower and upper limits of the 80% CI.

## 10.9. Analysis of safety

The analysis will be based on the Safety Sets.

### 10.9.1. Analysis of extent of exposure

The frequency and percentage of exposed subjects will be summarized overall and by study group.

### 10.9.2. Analysis of local and systemic adverse events

All solicited AEs will be summarized according to defined severity grading scales (see Table 12).

Frequencies and percentages of subjects experiencing each AE will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic AE overall and at each time point will also be presented. Local AEs will be assessed according to which vaccine was administered and the site of administration (e.g. upper or lower deltoid and the arm used for administration).

Post-vaccination solicited AEs reported from day 1 to day 7 will be summarized for the intervals days 1 to 3, days 4 to 7, and days 1 to 7 by maximal severity and by study group, excluding the 30-minute post-vaccination measurement, which will be summarized separately. In addition, solicited AEs ongoing after day 7 will be presented as unsolicited AEs.

Body temperature will be classified as <38°C (no fever) and ≥38°C (fever), as well as by 0.5°C increments from 36.0°C up to ≥40°C.

Erythema, induration, and swelling will be categorized as none (<25 mm), 25 to 50 mm (mild), 51 to 100 mm (moderate), and >100 mm (severe local reactions). The severity of pain will be categorized as none, mild (transient with no limitation in normal daily activity), moderate (some limitation in normal daily activity), and severe (unable to perform normal daily activity).

If an AE occurs more than once for a subject, it will be counted in the summary only once, according to the maximal severity. Summary tables showing the occurrence of any local or systemic AEs overall will be presented.

### 10.9.3. Analysis of other adverse events

Unsolicited Adverse Events

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

All reported AEs, as well as AEs judged by the investigator as at least possibly related to study vaccine(s), will be summarized according to system organ class and preferred term within system organ class. These summaries will be presented by study group and by interval of study observation. When an AE occurs more than once for a subject, the maximal severity and strongest relationship to the study group will be counted.

Separate summaries will be produced for the following categories:

- SAEs
- AEs that are possibly or probably related to vaccine(s)
- AEs leading to withdrawal
- AEs leading to a medically attended visit
- AESI

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

## 10.10. Interpretation of analyses

All analyses will be descriptive.

## 10.11. 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.

### 10.11.1. Sequence of analyses

The final study analysis will only be performed when all data up to the end of the study will be available and cleaned. Individual data listings will be provided and a clinical study report will be written.

***Any outcome of exploratory testing will be reported in an annex/addendum to the final study report. (Amended 29 Aug 2018)***

### 10.11.2. Statistical considerations for interim analyses

Not applicable.

# 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 PPD 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 PPD. 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 PPD standards and data cleaning procedures.

While completed eCRFs are reviewed by a PPD 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

Subject Diaries will be the only source document allowed for solicited local and systemic AEs (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 AEs that were of concern to the subject.

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

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

The site must enter all readable entries in the Subject Diary into the eCRF, including those values that may be biologically implausible (e.g. body temperature: 400°C).

Any illegible or implausible data should be reviewed with the subject/parent(s)/LAR(s). If an underlying solicited or unsolicited AE is described on review with the subject, this should be described in the source document and reported as an unsolicited AE in the Adverse Event eCRF (e.g. if the subject above confirms body temperature of 40°C on the day in which body temperature: 400°C was written into his/her Subject Diary, this fever of 40°C should be recorded in the Adverse Event eCRF).

Any newly described safety information (including a solicited AE) must not be written into the Subject Diary and must be described in the study file as a verbally reported AE. Any AE reported in this fashion must be described as an unsolicited AE and therefore entered on the Adverse Event eCRF.

## 11.3. Study monitoring

PPD 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. By Source Data Verification 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 PPD 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.

PPD 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 PPD standards/procedures, otherwise, the minimum retention period will default to 25 years after completion of the study report.

The investigator/institution must notify PPD 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 and/or PPD 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 PCD and to have secondary endpoint disclosed at latest 12 months after the LSLV as described in the protocol.

As per EU regulation, summaries of the results of GSK interventional studies (Phase I-IV) in adolescent and adult populations conducted in at least 1 EU member state will be posted on publicly available European Medicines Agency 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.

PPD 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

Not applicable.

# 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

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# Appendix A LABORATORY ASSAYS

## Serum bactericidal assay using human complement (hSBA)

The functional measure of immunogenicity used in this study, serum bactericidal activity, 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.

Serum bactericidal activity against rMenB+OMV NZ, MenACWY, and MenABCWY will be determined by performing an assay using plasma or serum as the source of exogenous complement, and measuring hSBA titers using standardized procedures against a standard panel consisting of *Neisseria meningitidis* serogroup A, C, W-135, Y and serogroup B test strains following study vaccination.

Each of the serogroup B test strains measures bactericidal activity primarily directed against one of the major meningococcal antigens included in rMenB+OMV NZ and in the combination MenABCWY vaccine: strain M14459 measures serum bactericidal activity against the factor H binding protein variant 1.1; strain M07-0241084 measures bactericidal activity against Neisseria heparin binding antigen; strain 96217 measures bactericidal activity against antigen Neisserial adhesin A; and strain NZ98/254 measures activity against PorA P1.4, which is the immunodominant antigen in the OMV NZ vaccine component.

# 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 |
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# Appendix C AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

| GlaxoSmithKline Biologicals SA<br><br>Vaccines R &D<br>**Protocol Amendment 1** | |
|---|---|
| **eTrack study number and abbreviated title** | 208205 MENABCWY-016 (V102_19) |
| **EudraCT number** | 2017-005128-12 |
| **Amendment number:** | Amendment 1, substantial |
| **Amendment date:** | 15 May 2018 |
| **Co-ordinating author:** | PPD, Principal Medical Writer, PPD, for GSK Biologicals |

**Rationale/background for changes:**

- The protocol has been updated based on feedback received from the State Institute for Drug Control (SUKL) regarding contraception requirements, exclusion of other vaccines before and after study vaccine(s) administration, exclusion of subjects with medical bleeding conditions, and to indicate that paracetamol is the preferred antipyretic/analgesic.
- The distribution and return of Subject Diaries has been clarified.
- The protocol was updated to include the use of a pregnancy notification form and to clarify that paper pregnancy forms will be used.
- Clarifications have been made to the analysis population definitions and the modeling analysis plans.
- Other minor changes have been made to correct typos, and improve clarity and alignment within the document.

Minor administrative edits (e.g. typos, abbreviations) have not been listed here.

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

Glossary of terms:

(Note: The alphabetical order was updated in the main text.)

***Highly effective*** ~~Adequate~~ contraception:

***Highly effective contraceptive methods, defined as contraceptive methods with a failure rate of less than 1% per year according to the Pearl Index, when used consistently and correctly and in accordance with the product label, when applicable. These methods include:***

- ***combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:***
  - ***oral***
  - ***intravaginal (i.e. contraceptive vaginal ring)***
  - ***percutaneous delivery system (i.e. transdermal patch)***
- ***progestogen-only hormonal contraception associated with inhibition of ovulation:***
  - ***injectable***
  - ***implantable***
- ***intrauterine device***
- ***intrauterine hormone-releasing system***
- ***bilateral tubal occlusion***
- ***vasectomized partner (provided that partner is the sole sexual partner of the female subject and that the vasectomized partner has received medical assessment of the surgical success, i.e. documented sterility). The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination of the subject and/or semen analysis, or medical history interview provided by her or her partner.***
- ***sexual abstinence (defined as refraining from penile-vaginal intercourse during the entire period of risk associated with the study treatments). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of 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 estrogen 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.~~

***Highly effective*** ~~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.

Section 1.3.1 Risk assessment

| **Important potential/identified risk** | **Data/Rationale for risk** | **Mitigation strategy** |
|---|---|---|
| Investigational vaccine: ***rMenB+OMV NZ*** | | |
| Important identified risk:<br>**Fever** | Fever may occur following vaccination. Fever is listed in the rMenB+OMV NZ SmPC. | Any febrile illness constitutes a contraindication to administration of the vaccine at the time scheduled for vaccination (see Section 6.5). Prophylactic use of analgesic/antipyretic medications ***(preferably paracetamol)*** during the first 7 days after vaccination is allowed on a voluntary basis, but must be recorded in the source document and Concomitant Medications electronic case report form (eCRF) field (see Section 6.7.1). |
| Important potential risk:<br>**Decrease of immunogenicity secondary to prophylactic use of paracetamol** | Prophylactic use of paracetamol reduces the incidence and severity of fever without affecting the immunogenicity of either rMenB+OMV NZ or routine vaccines [Prymula, 2014]. The effect of antipyretics other than paracetamol on the immune response has not been studied. | Prophylactic use of analgesic/antipyretic medications ***(preferably paracetamol)*** to reduce febrile reactions during the first 7 days after vaccination is allowed on a voluntary basis, but must be recorded in the source document and Concomitant Medications eCRF field (see Section 6.7.1). |

Synopsis and Section 4.2 Inclusion criteria for enrollment

7. Female subjects of childbearing potential may be enrolled in the study, if the subject:

- has practiced ***highly effective*** ~~adequate~~ contraception for 30 days prior to vaccination, and
- has a negative pregnancy test on the day of vaccination, and
- has agreed to continue ***highly effective*** ~~adequate~~ contraception during the entire treatment period and for 2 months after completion of the vaccination series.

Please refer to the glossary of terms for the definition of ***highly effective*** ~~adequate~~ contraception.

Synopsis and Section 4.3 Exclusion criteria for enrollment

Each subject must not have:

(Note: These 2 new criteria have been added to the previous 23 exclusion criteria.)

***24. Administration of a vaccine not foreseen by the study protocol in the period starting 14 days (for inactivated vaccines), 28 days (for live vaccines), or 7 days (for influenza vaccines) before each dose and ending 14 days (for inactivated vaccines), 28 days (for live vaccines), or 7 days (for influenza vaccines) after each dose of study vaccine(s) administration.***

***25. Thrombocytopenia, bleeding disorders, or be receiving anticoagulant therapy.***

Synopsis and Section 5.5 Outline of study procedures

**Table 4 List of study procedures**

(Note: Bold italicized text could not be applied to the individual table cells. Cells that were edited are shaded in the excerpt below.)

| **Epoch** | ***Epoch 001*** | | | | | |
|---|---|---|---|---|---|---|
| **Type of contact** | **Visit 1** | **Safety call 1** | **Visit 2** | **Visit 3** | **Safety call 2** | **Visit 4** |
| **Time points** | **Day 1** | **Day 15** | **Day 31** | **Day 61** | **Day 75** | **Day 91** |
| **Sampling time points** | **Pre-Vacc 1** | | **Post-Vacc 1** | | | **Post-Vacc 2** |
| Distribution of pDiary | ○ | | | ○ [4,6] | | |
| Review of pDiary | | | ○ | ○ [4] | | ○ [4] |
| Return of pDiary | | | ○ [6] | ○ [4,6] | | ○ [4,6] |

[4]This study procedure will not be performed at this time point for the MenACWY group, administered only 1 dose of vaccine at Visit 1 (no Visit 3 performed)

***[6]Subjects who receive a single dose of MenACWY only will return their pDiary at Visit 2 (Day 31). All subjects in the other treatment groups will return their first pDiary at Visit 3 (Day 61) and will receive a second pDiary for the remainder of the study.***

○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
Pre-Vacc: pre-vaccination; Post-Vacc: post-vaccination

**Table 5 Intervals between study visits**

| Interval | Optimal length of interval | Allowed interval (Min – Max)[1] |
|---|---|---|
| Visit 1 (Day 1) → Safety call 1 (Day 15) | 14 days | 11 days – 17 days (Days 12 – 18) |
| Visit 1 (Day 1) → Visit 2 (Day 31) | 30 days | 23 days – 40 days (Days 24 – 41) |
| Visit 1 (Day 1) → Visit 3 (Day 61) | 60 days | 53 days – 70 days (Days 54 – 71) |
| Visit 3 (Day 61) → Safety call 2 (Day 75) | 14 days | 11 days – 17 days (Days 72 – 78) |
| Visit 3 (Day 61) → Visit 4 (Day 91) | 30 days | 23 days – 40 days (Days 84 – 101) |

[1]Safety call time intervals will not be used for the assessment of protocol deviations. ***The Study Day ranges shown in the table are based on optimal intervals; the actual Study Day ranges for Safety Call 2 and Visit 4 will be based on when Visit 3 occurs.***

Section 6.5 Contraindications to subsequent vaccination

The following events constitute contraindications to administration of MenABCWY, rMenB+OMV NZ, or MenACWY 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 Section 5.5).

- Body temperature elevation (i.e. fever) within 3 days prior to intended study vaccination. Fever is defined as temperature ≥38.0°C.
- Significant acute illness (e.g. acute sever***e*** febrile illness) within 7 days prior to vaccination.
- Administration of any other vaccine 14 days (for inactivated vaccines)***,*** ~~or~~ 28 days (for live vaccines)***, or 7 days (for influenza vaccines)*** prior to vaccination~~, with the exception of flu vaccination~~.

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

(Note: Only the bullet point text was added to the synopsis.)

- ***A vaccine not foreseen by the study protocol administered during the period of 14 days (for inactivated vaccines), 28 days (for live vaccines), or 7 days (for influenza vaccines) before or after administration of the study vaccine(s) at Visit 1 and Visit 3*.***

  ****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 SmPC and according to local governmental recommendations and provided a written approval of the sponsor is obtained.***

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

***For analysis purposes, intercurrent conditions will be identified using AEs reported in the eCRFs during the study.***

Section 8.1.3.3 Other solicited adverse events

The use of analgesics/antipyretics ***(preferably paracetamol)*** for either prophylactic or treatment purposes will also be recorded as other solicited events in the Subject Diary and verified onto specific eCRFs and subject medical records.

Section 8.2.1 Pregnancy

Note: The pregnancy itself should always be recorded on ***a paper*** ~~an electronic~~ pregnancy report.

Section 8.3.3.2.1 Assessment of intensity

**Table 12 Intensity scales for solicited symptoms**

Note: Temperature will be recorded in the evening. If additional temperature measurements are to be performed at other times of the day, the highest temperature ~~and the time when the temperature was~~ measured will be recorded in the eCRF.

Section 8.4.1 Prompt reporting of serious adverse events, pregnancies, and other events

**Table 13 Timeframes for submitting serious adverse event, pregnancy, and other events reports**

| 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* | ***paper pregnancy notification report*** ~~electronic pregnancy report~~ | 2 weeks* | ***paper pregnancy follow-up report*** ~~electronic pregnancy report~~ |
| AESIs | 24 hours**‡ | electronic Expedited Adverse Events Report | 24 hours* | electronic Expedited Adverse Events Report |

Section 8.4.4 Completion and transmission of pregnancy reports

Once the investigator becomes aware that a subject is pregnant, the investigator (or designate) must complete the required information onto the ***paper*** ~~electronic~~ pregnancy report WITHIN 2 WEEKS. ***The investigator (or designate) must complete and fax a pregnancy notification form to PPD Pharmacovigilance (at*** PPD ***) after entering or updating information within the pregnancy eCRF.***

Section 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 PPD using the ***paper*** ~~electronic~~ pregnancy report and the Expedited Adverse Events Report if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

Synopsis and Section 10.2 Secondary endpoints

Safety Endpoints

- Unsolicited ~~local and systemic~~ AEs in all study groups
- ~~Adverse events,~~ SAEs, medically attended AEs, AEs leading to withdrawal, and AESIs, in all study groups from informed consent signature to Visit 4 (Day 91)

Section 10.4.3.2 Unsolicited Safety Set (unsolicited adverse events)

All subjects in the All Exposed Set ***who attended at least 1 visit or had at least 1 safety call or at least 1 follow-up event (such as withdrawal from the study) after receiving any study vaccination*** ~~with unsolicited AE data~~.

Section 10.4.4.1 Full Analysis Set 1

All subjects in the All Exposed Set who provided evaluable serum samples and whose assay results are available for at least 1 serogroup at Visit 4 ***for all study groups except the MenACWY group, or at Visit 2 for the MenACWY group***.

Section 10.4.4.2 Full Analysis Set 2

All subjects in the All Exposed Set who provided evaluable serum samples and whose assay results are available for at least 1 serogroup at Visit 2 ***for all study groups except the MenACWY group***.

Section 10.4.4.3 Full Analysis Set 3

All subjects in the All Exposed Set who provided evaluable serum samples and whose assay results are available for at least 1 serogroup at Visit 4 ***for all study groups except the MenACWY group, or at Visit 2 for the MenACWY group,*** and at baseline ***for all study groups***.

Section 10.4.4.4 Full Analysis Set 4

All subjects in the All Exposed Set who provided evaluable serum samples and whose assay results are available for at least 1 serogroup at Visit 2 and at baseline ***for all study groups except the MenACWY group***.

Section 10.5 Derived and transformed data

- Reactogenicity and Safety
  - Handling of missing data: ***for safety analyses, subjects who missed reporting symptoms (solicited/unsolicited) or concomitant medications will be analyzed further***. ***The main safety analyses will contain missing data (missing safety values will not be imputed) but further analyses to assess the missing mechanism will be specified in the statistical analysis plan.*** ~~subjects who missed reporting symptoms (solicited/unsolicited or concomitant medications) will be treated as subjects without symptoms (solicited/unsolicited or concomitant medications, respectively). In case of significant non-compliance with study procedures for reporting symptoms, the statistical analysis plan will be reassessed to ensure more accurate reporting of study data by further analysis~~.

Section 10.7 Analysis of immunogenicity

Analysis of hSBA GMT

An analysis of covariance (ANCOVA) model will be used to analyze post-vaccination log-transformed titers of hSBA for both the primary and secondary objectives (i.e. the hSBA at 1 month after the last vaccination and the hSBA at 1 month after the first vaccination, respectively). ***The ANCOVA model will be fitted to each serogroup/strain individually, and in addition the serogroup B strains will be grouped together to perform a pooled analysis.*** The GMTs obtained through the ANCOVA model will be called "adjusted" and the "unadjusted" GMTS will be obtained through descriptive statistics. Unadjusted and adjusted GMTs and associated 2-sided 80% CIs will be computed for each study group and for each strain at each visit. The fixed-effect model will include the age strata, treatment, serogroup, and center as fixed effects. The pre-vaccination log-transformed titer with centering at zero will be included as a continuous covariate. An interaction between serogroup and pre-vaccination log-transformed titer centered at zero will be included in the model. For each study group, adjusted GMTs and their 80% CIs will be obtained by exponentiating (base 10) the least squares means and the lower and upper limits of the 80% CIs of the log-transformed titers (base 10).

Section 10.7 Analysis of immunogenicity

Analysis of Percentage of Subjects With Titers Above LLOQ and a 4-fold Increase

***The fixed-effect model for the individual serogroups/strains will include the age strata, treatment, and center as fixed effects.*** The fixed-effect model ***for the pooled analysis*** will include ***the*** age strata, treatment, ***strain*** ~~serogroup~~, and center as fixed effects. The pre-vaccination log-transformed titer with centering at zero will be included as a continuous covariate. An interaction between serogroup and pre-vaccination log-transformed titer centered at zero will be included in the model.

Section 10.8.2 Analysis of local and systemic adverse events

(Note: The greater than or equal to sign [≥] has been edited to a greater than [>] sign in the first sentence.)

Erythema, induration, and swelling will be categorized as none (<25 mm), 25 to 50 mm (mild), 51 to 100 mm (moderate), and >≥100 mm (severe local reactions). The severity of pain will be categorized as none, mild (transient with no limitation in normal daily activity), moderate (some limitation in normal daily activity), and severe (unable to perform normal daily activity).

| GlaxoSmithKline Biologicals SA<br><br>Vaccines R &D<br>**Protocol Amendment 2** | |
|---|---|
| **eTrack study number and abbreviated title** | 208205 MENABCWY-016 (V102_19) |
| **EudraCT number** | 2017-005128-12 |
| **Amendment number:** | Amendment 2, substantial |
| **Amendment date:** | 29 August 2018 |
| **Co-ordinating author:** | PPD Principal Medical Writer, PPD, for GSK Biologicals |

**Rationale/background for changes:**

- A tertiary objective was added to allow potential exploratory evaluation of immune responses induced by the study vaccine(s) against a panel of strains of *Neisseria* species in a subset of subjects.
- Protocol Clarification Letter 1 was incorporated, which removed reference to a pregnancy electronic case report form.
- The window for Subject Diary reminder calls was clarified.
- Other minor changes were made to correct typos, and improve clarity and alignment within the document.

Minor administrative edits (e.g. typos, abbreviations) have not been listed here.

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

Synopsis, Objectives

***Tertiary***

- ***To further characterize the immune response induced by the study vaccine(s) against an additional panel of strains of Neisseria species in a subset of subjects.***

***Note: This tertiary objective is exploratory and suitable assays may or may not be developed. The tertiary objective will be assessed in a subset of subjects using remaining serum after the primary and secondary analyses have been completed; no additional blood samples will be collected from subjects. Any outcome of exploratory testing that would be of scientific/medical relevance will be reported in an annex/addendum to the final study report.***

Synopsis, Method of evaluation

***Tertiary***

- ***Endpoints related to the tertiary objective will be described in a separate statistical analysis plan.***

Section 2.3 Tertiary objective (newly added header and section)

## *2.3 Tertiary objective*

- ***To further characterize the immune response induced by the study vaccine(s) against an additional panel of strains of Neisseria species in a subset of subjects.***

***Note: This tertiary objective is exploratory and suitable assays may or may not be developed. The tertiary objective will be assessed in a subset of subjects using remaining serum after the primary and secondary analyses have been completed; no additional blood samples will be collected from subjects. Any outcome of exploratory testing that would be of scientific/medical relevance will be reported in an annex/addendum to the final study report.***

***Refer to Section 10.3 for the definition of the tertiary endpoint and to Section 10.11.1 for the reporting of tertiary endpoint results.***

Section 5.6.13.2.1 Subject diary reminder calls

Subject Diary reminder calls will be performed at 3 and 5 days ***(±1 day)*** after each vaccination ***(i.e., Day 4 and Day 6 after the first vaccination and accordingly after the second vaccination)***. The purpose of this call is to remind the subject/subject's parent(s)/LAR(s) about completion of the Subject Diary. The call follows the Subject Diary Reminder Telephone Call Script provided to the site. The subject/subject's parent(s)/LAR(s) should be reminded to contact the site via the telephone number provided in the informed consent to discuss medical questions.

Section 8.4.4 Completion and transmission of pregnancy reports

Once the investigator becomes aware that a subject is pregnant, the investigator (or designate) must complete the required information onto the paper pregnancy report WITHIN 2 WEEKS. The investigator (or designate) must complete and fax a pregnancy notification form to PPD Pharmacovigilance (at PPD ) after entering or updating information within the ***paper*** pregnancy ***report*** ~~eCRF~~.

Section 10.3 Tertiary endpoint (newly added header and section; heading numbers were updated in subsequent sections accordingly)

## *10.3 Tertiary endpoint*

***Endpoints related to the tertiary objective will be described in a separate statistical analysis plan.***

Section 10.5.2 All Exposed Set

All subjects in the All Enrolled Set who receive ~~a~~ ***any*** study vaccination.

Section 10.5.4.1 Full Analysis Set 1

All subjects in the All Exposed Set who provided evaluable serum samples and whose assay results are available for at least 1 serogroup ***or B strain*** at Visit 4 for all study groups except the MenACWY group, or at Visit 2 for the MenACWY group.

Section 10.5.4.2 Full Analysis Set 2

All subjects in the All Exposed Set who provided evaluable serum samples and whose assay results are available for at least 1 serogroup ***or B strain*** at Visit 2 for all study groups except the MenACWY group.

Section 10.5.4.3 Full Analysis Set 3

All subjects in the All Exposed Set who provided evaluable serum samples and whose assay results are available for at least 1 serogroup ***or B strain*** at Visit 4 for all study groups except the MenACWY group, or at Visit 2 for the MenACWY group, and at baseline for all study groups.

Section 10.5.4.4 Full Analysis Set 4

All subjects in the All Exposed Set who provided evaluable serum samples and whose assay results are available for at least 1 serogroup ***or B strain*** at Visit 2 and at baseline for all study groups except the MenACWY group.

Section 10.11.1 Sequence of analyses

***Any outcome of exploratory testing will be reported in an annex/addendum to the final study report.***