CLINICAL STUDY PROTOCOL V102_15E1 Version 4

A Phase 2b Open-Label Multi-Center Study Assessing the Immunological Persistence of Antibodies at Approximately 2 years After the last Meningococcal Vaccination in Study V102_15 and the Response to a Booster dose of GSK MenABCWY or Meningococcal Serogroup B Vaccines, in Healthy Adolescents

Trial to Assess Long-Term Persistence of Antibodies after GSK Meningococcal ABCWY Vaccination and Response to a Booster in Adolescents

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PROTOCOL SYNOPSIS V102_15E1

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
GlaxoSmithKline Vaccines	V102_15E1	GSK Meningococcal ABCWY Vaccine (MenABCWY) and GSK Meningococcal B Recombinant vaccine (rMenB+OMV)

Title of Study:

A Phase 2b, Open-Label, Multi-Center Study Assessing the Immunological Persistence of Antibodies at Approximately 2 years After the last Meningococcal Vaccination in Study V102_15 and the Response to a Booster dose of GSK MenABCWY or Meningococcal Serogroup B Vaccines, in Healthy Adolescents

Study Period: 180 days for follow-on subjects and 240 days for naive subjects	**Clinical Phase:** 2b

Background and Rationale: *Neisseria meningitidis* is a leading cause of bacterial meningitis and sepsis worldwide, capable of causing outbreaks and epidemics of invasive disease. Based on antigenic differences in their capsular polysaccharide, 13 serogroups of *N. meningitidis* have been identified. Virtually all disease-associated isolates are encapsulated, with serogroups A, B, C, W and Y being responsible for the large majority of invasive meningococcal infections worldwide.

The best option for the control of meningococcal disease is the use of effective vaccines that would include all five of the most common serogroups responsible for invasive disease. To meet this health need, GlaxoSmithKline Vaccines is currently developing a Meningococcal ABCWY vaccine (formerly developed by Novartis Vaccines) for adolescents and adults. In the phase 2 clinical program, several formulations of the candidate vaccine (with different amounts of Outer Membrane Vesicles (OMV) and recombinant MenB proteins) were tested and found to be well-tolerated and immunogenic. GSK performed a schedule-finding study for the MenABCWY vaccine (V102_15) in healthy adolescents aged 10 through 18 years. Subjects in this study have received either 2 doses of MenABCWY at different schedules (0,1months; 0,2 months; 0,6 months; 0,11 months), or 3 doses of MenABCWY (0,2,6 months), or 2 doses of the GSK Meningococcal Group B vaccine rMenB+OMV (at 0,2 months).

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
GlaxoSmithKline Vaccines	V102_15E1	GSK Meningococcal ABCWY Vaccine (MenABCWY) and GSK Meningococcal B Recombinant vaccine (rMenB+OMV)

One concern previously raised by CBER regarding the MenABCWY vaccine, was whether a 3-dose regimen is required to achieve an optimal immune response. The immediate responses to a 3-dose and 2-dose series are being assessed in the parent V102_15 study, as well as in other phase 2 studies, V102_16 and V102_16E1. However, to determine whether a 3-dose regimen provides any long-lasting benefit, GSK also plans to explore long-term persistence after 2 or 3 doses of the MenABCWY vaccine.

The planned extension study is ***primarily*** designed to compare the ***persistence*** of 2 ***doses*** (0,2 month ***or 0,6 month schedules***) or 3 ***doses*** (0,2,6 month s***chedule***) of the GSK MenABCWY vaccine ***or 2 doses (0,2 month schedule) of GSK rMenB+OMV vaccine*** administered to healthy adolescents at ***approximately*** 24 months after the last meningococcal vaccination in ***the parent study*** V102_15, ***compared with baseline antibody levels in vaccine naïve subjects of similar age at enrolment, as measured by*** automated Serum Bactericidal Assay with exogenous human complement ***(high-throughput*** hSBA ***[***HT-hSBA***]***). ***The r***esponse to a booster dose of MenABCWY ***or rMenB+OMV*** vaccine***s*** will also be assessed in follow-on subjects who received 2 or 3 doses of MenABCWY (at 0,2-, 0,6- or 0,2,6-month schedules), ***or 2 doses of rMenB+OMV, respectively,*** in the parent study, and will be compared with responses to a single dose of MenABCWY ***or rMenB+OMV, respectively,*** in ***vaccine*** naive subjects. ***Vaccine n***aive subjects will receive 2 doses of MenABCWY or rMenB+OMV, in order to complete the schedule of treatment. All subjects will be followed for 6 months after last vaccination for safety.

(Amended 4 April 2018)

Study Objectives:

***Primary* Immunogenicity Objectives**

1. To assess the persistence of bactericidal antibodies in subjects who previously received 2 or 3 doses of MenABCWY (administered according to 0, 2-, 0, 6- and 0, 2, 6-month schedules) or 2 doses of rMenB+OMV (given at a 0, 2-month schedule), at 24 months after the last meningococcal vaccination in study V102_15 compared with baseline antibody levels in meningococcal naive subjects at enrolment, as measured by percentages of subjects with HT-hSBA titers ≥ LLOQ and HT-hSBA GMTs against *N. meningitidis* test strains for serogroup B[1] and serogroups A, C, W, and Y.

(Amended 4 April 2018)

Secondary Immunogenicity Objectives

1. To assess the immune response at Day 31 after a booster dose of the MenABCWY vaccine given 24 months after last meningococcal vaccination in subjects who previously received 2 or 3 doses of MenABCWY at different schedules (administered according to 0, 2-, 0, 6- and 0, 2, 6-month schedules) in study V102_15 compared with the immune response at Day 31 after a single dose of MenABCWY in naive subjects, as measured by percentages of subjects with HT-hSBA titers ≥ LLOQ, percentages of subjects with four-fold rise[2] in titers and HT-hSBA GMTs against *N. meningitidis* serogroups A, C, W, Y and serogroup B test strains[1];

2. To assess the immune response at Day 1 (prevaccination), and at Day 6 and Day 31 after a booster dose of MenABCWY given at 24 months after last meningococcal vaccination in subjects who previously received 2 or 3 doses of MenABCWY at different schedules (administered according to 0, 2-, 0, 6- and 0, 2, 6-month schedules) in study V102_15, and at Day 1 (prevaccination) and after 2 doses of MenABCWY (at Day 66 and Day 91) in naive subjects, as measured

[1] Serogroup B test strains to be used in the study: M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA) and M07-0241084 (NHBA).

[2] For subjects with prevaccination hSBA titers < LLOQ, a post-vaccination hSBA ≥ 4 times the LLOQ; for subjects with prevaccination hSBA titers ≥ LLOQ, an increase of at least 4 times the prevaccination hSBA.

by percentages of subjects with HT-hSBA titers ≥ LLOQ, percentages of subjects with four-fold rise[1] in titers and HT-hSBA GMTs against *N meningitidis* serogroups A, C, W, Y and serogroup B test strains[2];

3. To assess the immune response at Day 31 after a booster dose of the rMenB+OMV vaccine given 24 months after last meningococcal vaccination in subjects who previously received 2 doses of rMenB+OMV administered according to 0, 2-month schedule in study V102_15 compared with the immune response at Day 31 after a single dose of rMenB+OMV in naive subjects, as measured by percentages of subjects with HT-hSBA titers ≥ LLOQ, percentages of subjects with four-fold rise[1] in titers and HT-hSBA GMTs against *N. meningitidis* serogroup B test strains[2];

4. To assess the immune response at Day 1 (prevaccination), and at Day 6 and Day 31 after a booster dose of the rMenB+OMV vaccine given 24 months after last meningococcal vaccination in subjects who previously received 2 doses of rMenB+OMV at 0, 2-month schedule in study V102_15, and at Day 1 (prevaccination) and after 2 doses of rMenB+OMV (at Day 66 and Day 91) in naive subjects, as measured by percentages of subjects with HT-hSBA titers ≥ LLOQ, percentages of subjects with four-fold rise[1] in titers and HT-hSBA GMTs against *N. meningitidis* serogroup B test strains[2].

(Amended 4 April 2018)

Secondary Safety Objectives

1. To evaluate safety and reactogenicity of a booster dose of MenABCWY given24 months after last meningococcal vaccination in subjects who previously received 2 or 3 doses of MenABCWY at different schedules (administered according to 0, 2-, 0, 6- and 0, 2, 6-month schedules) in study V102_15, and after a first dose of MenABCWY in naive subjects;
2. To evaluate safety and reactogenicity of a booster dose of rMenB+OMV given 24 months after last meningococcal vaccination in subjects who previously received 2 doses of rMenB (administered according to 0, 2-month schedule) in study V102_15 and after a first dose of rMenB+OMV in naive subjects;

[1] For subjects with prevaccination hSBA titers < LLOQ, a post-vaccination hSBA ≥ 4 times the LLOQ; for subjects with prevaccination hSBA titers ≥ LLOQ, an increase of at least 4 times the prevaccination hSBA.
[2] Serogroup B test strains to be used in the study: M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA) and M07-0241084 (NHBA).

3. To evaluate safety and reactogenicity of 2 doses of MenABCWY or rMenB+OMV in naive subjects.
Study Design: This is a phase 2b, open-label, multi-center extension of the study V102_15. There will be 4 follow-on groups in this extension study. Eligible follow-on subjects from the parent trial are those in groups ABCWY_0_2, ABCWY_0_6, ABCWY_0_2_6 and B_0_2, who have indicated willingness to participate in the extension at the time of termination from parent study, have received all planned meningococcal vaccinations in V102_15 (irrespective of administration within protocol-specified window), and have not received any additional meningococcal vaccinations since the last meningococcal vaccination in the V102_15 study. Up to 652 subjects who participated in the parent study V102_15 from Finland and Poland are eligible to be invited for enrolment in this extension study at approximately 24 months (-1/+3 months) after last meningococcal vaccination in the parent study. These subjects will be contacted by phone to check whether they are still interested in participating in the extension study, approximately 0-3 months prior to planned visit 1. All eligible subjects from Finland and Poland who are willing to participate in the extension study will be enrolled. Subjects will be analyzed in the vaccine groups that they were allocated to in the parent study. In addition, a newly enrolled Naive group will consist of 200 meningococcal vaccine-naive subjects of similar age, approximately 12 to 20 years old, to serve as a control for evaluating antibody persistence. Naive subjects are planned to be enrolled across all participating sites, based on the individual site's capacity to enroll. The number of Naive subjects enrolled per country will be proportional to the number of follow-on subjects enrolled from that country. Study groups: - ABCWY_ 0_2: subjects who received 2 doses of MenABCWY vaccine at Visit Month 0 and Visit Month 2 in study V102_15, and will receive 1 dose of MenABCWY in the extension study; - ABCWY_ 0_6: subjects who received 2 doses of MenABCWY vaccine at Visit Month 0 and Visit Month 6 in study V102_15, and will receive 1 dose of MenABCWY in the extension study; - ABCWY_0_2_6: subjects who received 3 doses of MenABCWY vaccine at Visit Month 0, Visit Month 2 and Visit Month 6 in study V102_15, and will receive 1 dose of MenABCWY in the extension study; - B_0_2: subjects who received 2 doses of rMenB+OMV vaccine at Visit Month 0 and Visit Month 2 in study V102_15, and will receive 1 dose of rMenB+OMV in the extension study; - Naïve controls: approximately 200 subjects who are meningococcal vaccine-naive and of similar age to subjects enrolled from the parent study,

approximately 12 to 20 years old, and will receive either 2 doses of MenABCWY or rMenB+OMV in the extension study.

Table 1: Study Groups in V102_15E1

V102_15 (Primary Study)		V102_15E1 ~24 months after last meningococcal vaccination in parent study	
Group	**Vaccine (schedule)**	**Group**	**Number of Subjects***
ABCWY_0_2	MenABCWY (0, 2 months)	ABCWY_0_2	up to 196
ABCWY_0_2_6	MenABCWY (0, 2, 6 months)	ABCWY_0_2_6	up to 130
B_0_2	rMenB+OMV (0, 2 months)	B_0_2	up to 196
ABCWY_0_6	MenABCWY (0, 6 months)	ABCWY_0_6	up to 130
		Naive (freshly enrolled)	200

*Maximum enrolment derived from planned enrolment per group in parent trial

Duration of the study: The study duration is 180 days for all follow-on subjects, and 240 days for naive subjects.

Data collection: eDiary; electronic Case Reporting Form (eCRF).

The study comprises 3 clinic visits (at ***D***ays 1, 6 and 31) and 3 safety phone calls (at ***D***ays 16, 91 and 181) for follow-on subjects, as detailed in Table 2.

Table 2: V102_15E1 Blood Draw and Vaccination Schedule for follow-on subjects

Group	Target enrolment	Day 1		Day 6	Day 16	Day 31		Day 91	Day 181
		Blood Draw	Vaccination	Blood Draw		Blood Draw			
ABCWY_0_2	100	20 mL	MenABCWY	20 mL	Safety Phone call	20 mL	Safety Evaluation	Phone Call for Safety Assessment	Phone Call for Safety Assessment and Study Termination
B_0_2	100	20 mL	rMenB+OMV	20 mL		20 mL			
ABCWY_0_2_6	100	20 mL	MenABCWY	20 mL		20 mL			
ABCWY_0_6	100	20 mL	MenABCWY	20 mL		20 mL			

Naive subjects will have 5 clinic visits (at ***D***ays 1, 31, 61, 66 and 91) and 4 safety phone calls (at ***D***ays 16, 76, 151 and 241), as detailed in Table 3.

Table 3: V102_15E1 Blood Draw and Vaccination Schedule for Naive subjects

	N	Day 1		Day 16	Day 31	Day 61	Day 66	Day 76	Day 91		Day 151	Day 241
		Blood Draw	Vaccination		Blood Draw	Vaccination	Blood Draw		Blood Draw			
Naive_ABCWY	100	20 mL	MenABCWY	Safety Phone call	20 mL	MenABCWY	20 mL	Safety Phone call	20 mL	Safety Evaluation	Phone Call for Safety Assessment	Phone Call for Safety Assessment and Study Termination
Naive_B	100	20 mL	rMenB+OMV		20 mL	rMenB+OMV	20 mL		20 mL			

On Day 1, subjects will be enrolled after screening for eligibility and having their medical history evaluated (since birth for naive subjects and since end of study V102_15 for follow-on subjects). All subjects will have approximately 20 mL of blood drawn after enrolment and vaccinated as detailed in Tables 2 and 3.

Number of Subjects planned: Up to 852 subjects may be enrolled into this study, including up to 652 follow-on subjects from the parent V102_15 study and 200 vaccine-naive subjects of similar age to the follow-on subjects.

Study Population and Subject Characteristics:

Subjects will be included in the study if in good health as judged by physical examination and medical history and if they meet all specified eligibility criteria.

Inclusion criteria: Adolescents from 12-20 years of age, generally in good health, and available for all study visits, who/whose legally acceptable representative has given written informed consent at the time of enrollment. Female subjects of childbearing potential must have a negative urine pregnancy test.

Exclusion criteria: For all subjects: Serious, acute, or chronic illnesses. Previous or suspected disease caused by *N. meningitidis*. Exposure to individuals with clinically proven meningococcal disease or clinical bacterial meningitis without further microbiologic characterization.

Follow on subjects from V102_15 study: Subjects previously enrolled in study V102_15 in Poland and Finland who have received all planned meningococcal vaccinations in the study and who have not received any additional meningococcal vaccination since the last meningococcal vaccination administered in the parent trial.

Naive subjects: Previous immunization with any meningococcal vaccine.

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

Study Procedures:

The study comprises 3 clinic visits (at ***D***ays 1, 6 and 31) and 3 safety phone calls (at ***D***ays 16, 91 and 181) for follow-on subjects. Naive subjects will have 5 clinic visits (at ***D***ays 1, 31, 61, 66 and 91) and 4 safety phone calls (at ***D***ays 16, 76, 151 and 241).

Written informed consent and, if applicable, written assent will be obtained before conducting any study-specific procedures.

Blinding: All subjects will receive the vaccine as an open label manner.

Blood sample: Collected prior to vaccination. 3 samples for follow-on subjects– 20 mL at Day 1, Day 6 and Day 31. For naive subjects 4 samples of 20 ml each will be collected – at Day 1, Day 31, Day 66 and Day 91.

Data collection: eDiary for local and systemic reactions; Electronic Case Reporting Form (eCRF)

Clinic visits: At ***D***ay 1, subjects will be assessed for eligibility and then enrolled into the study. After signing informed consent (and/or assent, as applicable), subjects will undergo a review of medical history and prior medications/vaccinations (since end of study V102_15 for follow-on subjects and since birth for naive subjects), and a physical assessment. All newly recruited subjects will be in the naive group and these will be randomized 1:1 to receive MenABCWY or rMenB+OMV using IRT. No randomization to treatment arm for follow-on subjects is required as vaccine groups remain the same as in the parent study V102_15; however, allocation of treatment will be done using IRT. A blood sample of ~20 mL will be collected at Day 1 from all subjects.

Follow-on subjects will also have a clinic visit at Day 6 for a blood draw of 20 mL. At ***D***ay 31, all subjects will have a 20 mL blood draw and a safety evaluation. Naive subjects will receive their second dose of MenABCWY or rMenB+OMV at ***D***ay 61 to complete the series, and have 2 subsequent blood draws at ***D***ays 66 and 91. ***See Table 4 for testing schedules.***

Table 4: Sample Testing Schedule in V102_15E1

Assay Type	*Subject pool*	*V102_15E1 (extension study)*				
		Day 1	*Day 6*	*Day 31*	*Day 66*	*Day 91*
HT-hSBA (all enrolled)	*Follow-on*	√	√	√		
	Naive	√		√	√	√

HT-hSBA = high-throughput human serum bactericidal assay

All subjects will be followed for 6 months after last vaccination for safety and then terminated from the study in a safety phone call.

Vaccination: At Day1, follow-on subjects from the ABCWY_0_2, ABCWY_0_6, and ABCWY_0_2_6 groups will receive 1 booster dose of MenABCWY. Subjects from the B_0_2 group will receive a booster dose of rMenB+OMV. Naive subjects will be randomized 1:1 to receive either 2 doses of MenABCWY or 2 doses of rMenB+OMV at Day 1 and at Day 61.

Safety Assessment: After vaccination at ***D***ay 1 (and ***D***ay 61 for naive subjects), subjects or their parents/legal guardians will be observed for at least 30 minutes at the clinic, and instructed to record any local and systemic AEs for 7 days after vaccination using eDiary. Unsolicited AEs will be collected for 1 month after each vaccination. SAEs, medically attended AEs and AEs leading to withdrawal will be collected for the duration of the study (180 days for follow-on subjects and 240 days for naive). Final safety assessment will be performed at Day 181 for follow-on subjects and Day 241 for naive subjects via a phone call.

Study termination: Subjects in the follow-on groups will be terminated after final safety assessment at ***D***ay 181, while subjects in the Naive group will be terminated after final safety assessment at Day 241.

Randomization: an Interactive Response Technology (IRT) will be used in the study. The following randomization process will be used in this study.

1. Randomization into the treatment group only for the Naive group subjects

At Visit Day 1, prior to the study vaccination, naive subjects will be randomized into the 2 study groups according to a 1:1 ratio, MenABCWY: rMenB+OMV.

(Amended 4 April 2018)

Study Vaccines:

GSK Meningococcal ABCWY Vaccine (MenABCWY): Fixed-combination vaccine obtained by reconstitution and extemporaneous mixing of lyophilized MenACWY powder with liquid rMenB + OMV suspension for injection in deltoid muscle. The total volume for injection is ≥ 0.5mL of solution.

GSK Meningococcal B Recombinant vaccine (rMenB+OMV): Each dose contains recombinant *Neisseria meningitidis* group B NHBA fusion protein (50µg), Recombinant *Neisseria meningitidis* group B NadA protein (50µg), Recombinant *Neisseria meningitidis* group B fHbp fusion protein (50µg), Outer membrane vesicles (OMV) from *Neisseria meningitidis* group B strain NZ98/254 (25µg) and Aluminum hydroxide (1.5 mg). Vaccine supplied as a single 0.5 mL dose administered IM into the deltoid area according to the relevant EU and US Summary of Product Characteristics.

Endpoint(s):

Primary *Immunogenicity Endpoints*

The following will be summarized at 24 months after last meningococcal vaccination for all follow-on subjects and at Day 1 in extension study for naive subjects

1. Percentages of subjects with HT-hSBA titers ≥ LLOQ against each of four serogroup B test strains,[1] and serogroups A, C, W and Y ***(only for MenABCWY groups).***

2. HT-hSBA GMTs against each of four serogroup B test strains,[1] and against *N. meningitidis* serogroups A, C, W and Y ***(only for MenABCWY groups).***

[1] Serogroup B test strains to be used in the study: M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA) and M07-0241084 (NHBA).

Secondary Immunogenicity Endpoint(s)

The following will be summarized at Days 1 (except four-fold rise), 6 and 31 for follow-on subjects, and at Days 1, 31, 66 and 91 for naive subjects

1. Percentages of subjects with HT-hSBA titers ≥ LLOQ and differences between groups against each of four serogroup B test strains[1] and serogroups A, C, W and Y (only after MenABCWY vaccination)

2. HT-hSBA GMTs and group ratios against each of four serogroup B test strains[1] and serogroups A, C, W and Y (only after MenABCWY vaccination), and GMRs (Day 6/Day1 and Day 31/Day 1 for follow-on subjects; Day 31/Day 1, Day 66/Day 1 and Day 91/Day 1 for naive subjects)

3. Percentages of subjects with four-fold rise[2] in HT-hSBA titers and group differences, against each of four serogroup B test strains[1] and serogroups A, C, W and Y (only after MenABCWY vaccination).

(Amended 4 April 2018)

Safety Endpoint(s):

Safety of the study vaccines will be assessed in all subjects in terms of the percentages of subjects with reported adverse events including:

- Any solicited and unsolicited AEs reported within 30 minutes after vaccination at Day 1 (for all subjects) and also Day 61 (for naive subjects only);
- Solicited local and systemic AEs reported from Day 1 (6 hours) to Day *7* after vaccination at Day 1 (for all subjects) and Day 61 (for naive subjects);
- Other indicators of reactogenicity (e.g. use of analgesics / antipyretics, body temperature) within 7 days after vaccination at Day 1 (for all subjects) and Day 61 (for naive subjects);
- Unsolicited AEs reported from Day 1 to Day 31 for all subjects and Day 61 to Day 91 for naive subjects;

[1] Serogroup B test strains to be used in the study: M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA) and M07-0241084 (NHBA).

[2] For subjects with prevaccination hSBA titers < LLOQ, a post-vaccination hSBA ≥ 4 times the LLOQ; for subjects with prevaccination hSBA titers ≥ LLOQ, an increase of at least 4 times the prevaccination hSBA.

- Medically-attended AEs reported during the entire study period (up to ***D***ay 181 for follow-on subjects and up to Day 241 for naive subjects);
- AEs leading to premature withdrawal from the study during the entire study period (up to ***D***ay 181 for follow-on subjects and up to Day 241 for naive subjects);

SAEs reported during the entire study period (up to ***D***ay 181 for follow-on subjects and up to Day 241 for naive subjects).

Statistical Analyses:

Primary *immunogenicity objective*

The proportion of subjects with HT-hSBA titers ≥ LLOQ against *N. meningitidis* serogroup B test strains[1] and serogroups A, C, W and Y and associated two-sided 95% Clopper- Pearson confidence intervals (CI) will be calculated for each vaccine group ***at Day 1 (i.e. 24 months after the last meningococcal vaccination in study V102_15 for follow-on subjects and Day 1 for naïve subjects). The CIs for the rate difference will be constructed using the method of Miettinen and Nurminen.***

HT-hSBA GMTs at Day 1 and associated two-sided 95% CIs against N meningitidis serogroups A, C, W and Y and each of four serogroup B test strains[1] will be calculated for each vaccine group using an Analysis of Variance (ANOVA) to account for imbalance of explanatory variables. Between-group ratios of GMTs will be computed and 95% confidence intervals will be calculated by exponentiating the between-group difference in the least square means (from the ANOVA) of the log-transformed titers and the 95% CIs.

Secondary immunogenicity objective(s)

The proportion of subjects with HT-hSBA titers ≥ LLOQ and with four-fold rise[2] in titers against N. meningitidis serogroup B test strains[1] and serogroups A, C, W and Y and associated two-sided 95% Clopper-Pearson (CI) will be calculated for each

[1] Serogroup B test strains to be used in the study: M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA) and M07-0241084 (NHBA).

[2] For subjects with prevaccination hSBA titers < LLOQ, a post-vaccination hSBA ≥ 4 times the LLOQ; for subjects with prevaccination hSBA titers ≥ LLOQ, an increase of at least 4 times the prevaccination hSBA.

vaccine group at Day 1 (except four-fold rise), Day 6 and Day 31 (follow-on) / Day 1 Day 66, and Day 91 (naïve). The proportion will also be computed for subjects positive for at least 1, at least 2, at least 3, and all 4 test strains.

For between-group comparisons of percentages of subjects with HT-hSBA titers ≥ LLOQ, and percentages of subjects with four-fold rise[1] in titers, estimates of the difference will be provided along with the associated 95% confidence interval using the methodology of Miettinen and Nurminen.

HT-hSBA GMTs and GMRs (post-vaccination / pre-vaccination) and associated two-sided 95% CIs against N meningitidis serogroups A, C, W and Y and each of four serogroup B test strains[2] will be calculated for each vaccine group using an Analysis of Variance (ANOVA) to account for imbalance of explanatory variables. Between-group ratios of GMTs and GMRs will be computed and 95% confidence intervals will be calculated by exponentiating the between-group difference in the least square means (from the ANOVA) of the log-transformed titers and the 95% CIs.

Secondary safety objectives

Further details on statistical analysis methods for safety can be found in section 8.4.3.1 .

(Amended 4 April 2018)

Interim Analysis: None planned. Data for all primary and secondary objectives will be analyzed and reported in a final CSR after primary testing and analysis are completed.

(Amended 4 April 2018)

Data Monitoring Committee: No Data Monitoring Committee will be utilized in this trial.

[1] For subjects with prevaccination hSBA titers < LLOQ, a post-vaccination hSBA ≥ 4 times the LLOQ; for subjects with prevaccination hSBA titers ≥ LLOQ, an increase of at least 4 times the prevaccination hSBA.
[2] Serogroup B test strains to be used in the study: M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA) and M07-0241084 (NHBA).

Table 5: Time and Events Table – Treatment Period-MenABCWY_0_2, MenABCWY_0_2_6, MenABCWY_0_6 and B_0_2 groups

	Visit Type	Screening	Clinic Visit	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Phone Call
	Study Day		1	6	16	31	91	181
	Visit Window (Days)	-5 to 1	~24 months after last meningococcal vaccination (-1/+3 months)	-1 to +3	-2/+2	-7 to +10	-14 to +14	-14 to +14
	Visit Interval			5 days after visit 1		30 days after visit 1		
	Visit Number	Pre-vaccination	1	2		3		
Study Event	**References**							
Study Treatment								
Vaccination	Section 5.2		X					
Screening and Safety								
Informed Consent [a]	Section 5.1.1	X						
Medical History	Section 5.1.2	X						
Physical Exam	Sections 5.1.2 and 5.3.1	X	X [b,c,d]			X[c]		

	Visit Type	Screening	Clinic Visit	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Phone Call
	Study Day		**1**	**6**	**16**	**31**	**91**	**181**
	Visit Window (Days)	**-5 to 1**	**~24 months after last meningococcal vaccination (-1/+3 months)**	**-1 to +3**	**-2/+2**	**-7 to +10**	**-14 to +14**	**-14 to +14**
	Visit Interval			**5 days after visit 1**		**30 days after visit 1**		
	Visit Number	**Pre-vaccination**	**1**	**2**		**3**		
Study Event	**References**							
Pregnancy Test	Sections 3.5 and 5.1.2	X	X [b,d]					
Exclusion/Inclusion Criteria	Section 4.	X	X[d]					
Randomization/Pack number allocation	Section 5.1.4		X [b]					
30 Minutes Post Injection Assessment	Section 5.2.1		X					
Subject eDiary Dispensed with Training	Section 5.2.1		X					

	Visit Type	Screening	Clinic Visit	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Phone Call
	Study Day		**1**	**6**	**16**	**31**	**91**	**181**
	Visit Window (Days)	**-5 to 1**	**~24 months after last meningococcal vaccination (-1/+3 months)**	**-1 to +3**	**-2/+2**	**-7 to +10**	**-14 to +14**	**-14 to +14**
	Visit Interval			**5 days after visit 1**		**30 days after visit 1**		
	Visit Number	**Pre-vaccination**	**1**	**2**		**3**		
Study Event	**References**							
Subject eDiary Reviewed and Collected	Section 5.3.1					X		
Assess all AEs	Section 7.1		X		X	X	X	X
Assess SAEs	Section 7.1.4		X		X	X	X	X
Assess for medically attended AEs, AEs leading to withdrawal,	Sections 7.1.4.1 and 7.1.3		X		X	X	X	X
Assess relevant medications	Sections 5.1.2 and 6.5	X	X[d]		X	X	X	X
Immunogenicity								

	Visit Type	Screening	Clinic Visit	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Phone Call
	Study Day		**1**	**6**	**16**	**31**	**91**	**181**
	Visit Window (Days)	**-5 to 1**	**~24 months after last meningococcal vaccination (-1/+3 months)**	**-1 to +3**	**-2/+2**	**-7 to +10**	**-14 to +14**	**-14 to +14**
	Visit Interval			**5 days after visit 1**		**30 days after visit 1**		
	Visit Number	**Pre-vaccination**	**1**	**2**		**3**		
Study Event	**References**							
Serology blood draw	Section 3.5		X [a]	X		X		
Study Termination								
Termination Procedures	Section 5.5							X[e]

Notes:
[a] Confirm consent form(s) signed prior to any procedures.
[b] Procedure to be performed prior to vaccination
[c] Symptom-directed physical examination
[d] Some procedures may not need to be repeated if screening is performed before Day 1. Inclusion/exclusion criteria should, however, be rechecked prior to vaccination even if performed before.
[e] Subjects who terminate early are recommended to complete certain study procedures. See section 5.5.1 for details.

Table 6: Time and Events Table – Treatment Period-NAÏVE groups

	Visit Type	Screening	Clinic Visit	Phone Call	Clinic Visit	Clinic Visit	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Phone Call
	Study Day		**1**	**16**	**31**	**61**	**66**	**76**	**91**	**151**	**241**
	Visit Window (Days)	**-5 to 1**	**n/a**	**-2/+2**	**-7 to +10**	**-7 to +10**	**-1 to +3**	**-2/+2**	**-7 to +10**	**-14 to +14**	**-14 to +14**
	Visit Interval				**30 days after visit 1**		**5 days after visit 3**		**30 days after visit 3**		
	Visit Number	**Pre-vaccination**	**1**		**2**	**3**	**4**		**5**		
Study Event	**References**										
Study Treatment											
Vaccination	Section 5.2		X			X					
Screening and Safety											
Informed Consent [a]	Section 5.1.1	X									
Medical History	Section 5.1.2	X									
Physical Exam	Sections 5.1.2 and 5.3.1	X	X [b,d]		X[c]	X[c]			X[c]		

	Visit Type	Screening	Clinic Visit	Phone Call	Clinic Visit	Clinic Visit	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Phone Call
	Study Day		**1**	**16**	**31**	**61**	**66**	**76**	**91**	**151**	**241**
	Visit Window (Days)	**-5 to 1**	**n/a**	**-2/+2**	**-7 to +10**	**-7 to +10**	**-1 to +3**	**-2/+2**	**-7 to +10**	**-14 to +14**	**-14 to +14**
	Visit Interval				**30 days after visit 1**		**5 days after visit 3**		**30 days after visit 3**		
	Visit Number	**Pre-vaccination**	**1**		**2**	**3**	**4**		**5**		
Study Event	**References**										
Pregnancy Test	Sections 3.5 and 5.1.2	X	X [b,d]			X[b,e]					
Exclusion/Inclusion Criteria	Section 4.	X	X[d]			X[d,e]					
Randomization/Pack number allocation	Section 5.1.4		X [b,c]			X [b,c]					
30 Minutes Post Injection Assessment	Section 5.2.1		X			X					
Subject eDiary Dispensed with Training	Section 5.2.1		X			X					

	Visit Type	Screening	Clinic Visit	Phone Call	Clinic Visit	Clinic Visit	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Phone Call
	Study Day		**1**	**16**	**31**	**61**	**66**	**76**	**91**	**151**	**241**
	Visit Window (Days)	**-5 to 1**	**n/a**	**-2/+2**	**-7 to +10**	**-7 to +10**	**-1 to +3**	**-2/+2**	**-7 to +10**	**-14 to +14**	**-14 to +14**
	Visit Interval				**30 days after visit 1**		**5 days after visit 3**		**30 days after visit 3**		
	Visit Number	**Pre-vaccination**	**1**		**2**	**3**	**4**		**5**		
Study Event	**References**										
Subject eDiary Reviewed and Collected	Section 5.3.1				X				X		
Assess all AEs	Section 7.1		X	X	X	X		X	X	X	X
Assess SAEs	Section 7.1.4		X	X	X	X		X	X	X	X
Assess for medically attended AEs, AEs leading to withdrawal	Sections 7.1.4.1 and 7.1.3		X	X	X	X		X	X	X	X
Assess relevant medications	Sections 5.1.2 and 6.5	X	X	X	X	X		X	X	X	X
Immunogenicity											

	Visit Type	Screening	Clinic Visit	Phone Call	Clinic Visit	Clinic Visit	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Phone Call
	Study Day		**1**	**16**	**31**	**61**	**66**	**76**	**91**	**151**	**241**
	Visit Window (Days)	**-5 to 1**	**n/a**	**-2/+2**	**-7 to +10**	**-7 to +10**	**-1 to +3**	**-2/+2**	**-7 to +10**	**-14 to +14**	**-14 to +14**
	Visit Interval				**30 days after visit 1**		**5 days after visit 3**		**30 days after visit 3**		
	Visit Number	**Pre-vaccination**	**1**		**2**	**3**	**4**		**5**		
Study Event	**References**										
Serology blood draw	Section 3.5		X [a]		X		X		X		
Termination Procedures	Section 5.5										X[f]

Notes:

[a] Confirm consent form(s) signed prior to any procedures.

[b] Procedure to be performed prior to vaccination

[c] Symptom-directed physical examination

[d] Some procedures may not need to be repeated if screening is performed before Day 1. Inclusion/exclusion criteria should, however, be rechecked prior to vaccination even if performed before.

[e] Subjects who terminate early are recommended to complete certain study procedures. See section 5.5.1 for details.

LIST OF ABBREVIATIONS

AE	Adverse Event
ANOVA	Analysis of Variance
CDM	Clinical Data Management
CI	Confidence Interval
CRM	Cross Reactive material
CRO	Contract Research Organization
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDT	Electronic Data Transfer
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
fHbp	Factor H Binding Protein
GCP	Good Clinical Practices
GMT	Geometric Mean Titer
GMR	Geometric Mean Ratio
hSBA	Human Serum Bactericidal Assay
HT-hSBA	High-Throughput Human Serum Bactericidal Assay
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IM	Intramuscular
IRB	Institutional Review Board
IRT	Interactive Response Technology
LSLV	Last Subject Last Visit
LLOQ	Lower Limit of Quantitation
MedDRA	Medical Dictionary for Regulatory Activities
NadA	Neisserial Adhesin A
NHBA	Neisseria Heparin Binding Antigen
PorA	Porin A
PPS	Per Protocol Set
PT	Preferred Term
RR	Relative Risk
SAE	Serious Adverse Event
SDA	Source Data Agreement
SOC	System Organ Class
SOP	Standard Operating Procedure

SmPC Summary of Product Characteristics

1. BACKGROUND AND RATIONALE

1.1 Background

Neisseria meningitidis is a leading cause of bacterial meningitis and sepsis worldwide, capable of causing outbreaks and epidemics of invasive disease. Based on antigenic differences in their capsular polysaccharide, 13 serogroups of *N. meningitidis* have been identified. Virtually all disease-associated isolates are encapsulated, with serogroups A, B, C, W and Y being responsible for the large majority of invasive meningococcal infections worldwide.

The best option for the control of meningococcal disease is the use of effective vaccines that would include all five of the most common serogroups responsible for invasive disease. To meet this health need, GlaxoSmithKline Vaccines is currently developing a Meningococcal ABCWY vaccine (formerly developed by Novartis Vaccines) for adolescents and adults. In the phase 2 clinical program, several formulations of the candidate vaccine (with different amounts of Outer Membrane Vesicles (OMV) and recombinant MenB proteins) were tested and found to be well-tolerated and immunogenic. GSK performed a schedule-finding study for the MenABCWY vaccine (V102_15) in healthy adolescents aged 10 through 18 years. Subjects in this study have received either 2 doses of MenABCWY at different schedules (0,1 months; 0,2 months; 0,6 months; 0,11 months), or 3 doses of MenABCWY (0,2,6 months), or 2 doses of the GSK Meningococcal Group B vaccine rMenB+OMV (at 0,2 months).

One concern previously raised by CBER regarding the MenABCWY vaccine, was whether a 3-dose regimen is required to achieve an optimal immune response. The immediate responses to a 3-dose and 2-dose series are being assessed in the parent V102_15 study, as well as in other phase 2 studies, V102_16 and V102_16E1. However, to determine whether a 3-dose regimen provides any long-lasting benefit, GSK also plans to explore long-term persistence after 2 or 3 doses of the MenABCWY vaccine, in this planned extension study.

Comprehensive reviews of MenABCWY and rMenB+OMV NZ are contained in the latest version of Investigator's Brochures (IB) supplied by GSK; these documents should be reviewed prior to initiating the study.

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

(Amended 4 April 2018)

1.2 Rationale

The planned extension study is primarily designed to compare the ***persistence*** of 2 ***doses*** (0,2 month~~s~~ ***or 0,6 month schedules***) or 3 ***doses*** (0,2,6 month~~s~~ ***schedule***) of the GSK MenABCWY vaccine ***or 2 doses (0,2 month schedule) of GSK rMenB+OMV vaccine*** administered to healthy adolescents at ***approximately*** 24 months after the last meningococcal vaccination in ***the parent study*** V102_15, ***compared with baseline antibody levels in vaccine naïve subjects of similar age at enrolment as measured by*** automated Serum Bacterial Assay with exogenous human complement ***(high-throughput*** hSBA ***[***HT-hSBA***]***). ***The response*** to a booster dose of MenABCWY ***or rMenB+OMV*** vaccine***s*** will also be assessed in follow-on subjects who received 2 or 3 doses of MenABCWY (at 0,2-, 0,6- or 0,2,6-month schedules), ***or 2 doses of rMenB+OMV, respectively,*** in the parent study, and will be compared with responses to a single dose of MenABCWY ***or*** MenB+OMV***, respectively, in vaccine*** naïve subjects. ***Vaccine n***aïve subjects will receive 2 doses of MenABCWY or rMenB+OMV, in order to complete the schedule of treatment. All subjects will be followed for 6 months after last vaccination for safety.

(Amended 4 April 2018)

2. OBJECTIVES

2.1 Primary *Immunogenicity* Objective(s)

1. ***To assess the persistence of bactericidal antibodies in subjects who previously received 2 or 3 doses of MenABCWY (administered according to 0, 2-, 0, 6- and 0, 2, 6-month schedules) or 2 doses of rMenB+OMV (given at a 0, 2-month schedule), 24 months after the last meningococcal vaccination in study V102_15 compared with baseline antibody levels in meningococcal naive subjects at enrolment, as measured by percentages of subjects with HT-hSBA titers ≥ LLOQ and HT-hSBA GMTs against N. meningitidis test strains for serogroup B[1] and serogroups A, C, W, and Y.***

(Amended 4 April 2018)

2.2 Secondary Objective(s)

2.2.1 Secondary Immunogenicity Objectives

1. To assess the immune response at Day 31 after a booster dose of the MenABCWY vaccine given 24 months after last meningococcal vaccination in subjects who previously received 2 or 3 doses of MenABCWY at different schedules (administered according to 0, 2-, 0, 6- and 0, 2, 6-month schedules) in study V102_15 compared with the immune response at Day 31 after a single dose of MenABCWY in naive subjects, as measured by percentages of subjects with HT-hSBA titers ≥ LLOQ, percentages of subjects with four-fold rise[2] in titers and HT-hSBA GMTs against *N. meningitidis* serogroups A, C, W, Y and serogroup B test strains[1];

2. To assess the immune response at Day 1 (prevaccination), and at Day 6 and Day 31 after a booster dose of MenABCWY given 24 months after last meningococcal vaccination in subjects who previously received 2 or 3 doses of MenABCWY at different schedules (administered according to 0, 2-, 0, 6- and 0, 2, 6-month schedules) in study V102_15, and at Day 1 (prevaccination) and after 2 doses of MenABCWY (at Day 66 and Day 91) in naive subjects, as measured by percentages of subjects with HT-hSBA titers ≥ LLOQ, percentages of subjects

[1] Serogroup test strains to be used in the study: M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA), and M07-0241084 (NHBA).

[2] For subjects with prevaccination hSBA titers < LLOQ, a post-vaccination hSBA ≥ 4 times the LLOQ; for subjects with prevaccination hSBA titers ≥ LLOQ, an increase of at least 4 times the prevaccination hSBA

with four-fold rise[1] in titers and HT-hSBA GMTs against *N meningitidis* serogroups A, C, W, Y and serogroup B test strains[2];

3. To assess the immune response at Day 31 after a booster dose of the rMenB+OMV vaccine given 24 months after last meningococcal vaccination in subjects who previously received 2 doses of rMenB+OMV administered according to 0, 2-month schedule in study V102_15 compared with the immune response at Day 31 after a single dose of rMenB+OMV in naive subjects, as measured by percentages of subjects with HT-hSBA titers ≥ LLOQ, percentages of subjects with four-fold rise[1] in titers and HT-hSBA GMTs against *N. meningitidis* serogroup B test strains[2];

4. To assess the immune response at Day 1 (prevaccination), and at Day 6 and Day 31 after a booster dose of the rMenB+OMV vaccine given 24 months after last meningococcal vaccination in subjects who previously received 2 doses of rMenB+OMV at 0, 2-month schedule in study V102_15, and at Day 1 (prevaccination) and after 2 doses of rMenB+OMV (at Day 66 and Day 91) in naive subjects, as measured by percentages of subjects with HT-hSBA titers ≥ LLOQ, percentages of subjects with four-fold rise[1] in titers and HT-hSBA GMTs against *N. meningitidis* serogroup B[2] test strains.

(Amended 4 April 2018)

2.2.2 Secondary Safety Objectives

1. To evaluate safety and reactogenicity of a booster dose of MenABCWY given 24 months after last meningococcal vaccination in subjects who previously received 2 or 3 doses of MenABCWY at different schedules (administered according to 0, 2-, 0, 6- and 0, 2, 6-month schedules) in study V102_15, and after a first dose of MenABCWY in naive subjects;
2. To evaluate safety and reactogenicity of a booster dose of rMenB+OMV given 24 months after last meningococcal vaccination in subjects who previously received 2 doses of rMenB (administered according to 0, 2-month schedule) in study V102_15 and after a first dose of rMenB+OMV in naive subjects;

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[1] For subjects with prevaccination hSBA titers < LLOQ, a post-vaccination hSBA ≥ 4 times the LLOQ; for subjects with prevaccination hSBA titers ≥ LLOQ, an increase of at least 4 times the prevaccination hSBA

[2] Serogroup B test strains to be used in the study: M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA), and M07-0241084 (NHBA)

3. To evaluate safety and reactogenicity of 2 doses of MenABCWY or rMenB+OMV in naive subjects.

(Amended 4 April 2018)

3. STUDY DESIGN

3.1 Overview of Study Design

Experimental design: Phase 2b, multi-center study in healthy adolescents 12-20 years with six study groups: four follow-on groups and 2 naïve groups.

Eligible follow-on subjects from the parent trial are those in groups ABCWY_0_2, ABCWY_0_6, ABCWY_0_2_6 and B_0_2, who have indicated willingness to participate in the extension at the time of termination from parent study, have received all planned meningococcal vaccinations in V102_15 (irrespective of administration within protocol-specified window), and have not received any additional meningococcal vaccinations since the last meningococcal vaccination in the V102_15 study. Up to 652 subjects who participated in the parent study V102_15 from Finland and Poland are eligible to be invited for enrolment in this extension study at approximately 24 months (-1/+3 months) after last meningococcal vaccination in the parent study. These subjects will be contacted by phone to check whether they are still interested in participating in the extension study, approximately 0-3 months prior to planned visit 1. All eligible subjects from Finland and Poland who are willing to participate in the extension study will be enrolled. Subjects will be analyzed in the vaccine groups that they were allocated to in the parent study. In addition, a newly enrolled Naive group will consist of 200 meningococcal vaccine-naive subjects of similar age, approximately 12 to 20 years old, to serve as a control for evaluating antibody persistence. Naive subjects are planned to be enrolled across all participating sites, based on the individual site's capacity to enroll. The number of Naive subjects enrolled per country will be proportional to the number of follow-on subjects enrolled from that country.

As a multicenter study, to ensure consistency of data, the participating staff will be trained in a uniform fashion and sites will be monitored to ensure consistency in study execution across all centers.

Duration of the study: The study duration is approximately 180 days for follow on subjects and 240 days for the naive subjects.

Study groups:

- ABCWY_ 0_2: subjects who received 2 doses of MenABCWY vaccine at Visit Month 0 and Visit Month 2 in study V102_15, and will receive 1 dose of MenABCWY in the extension study;
- ABCWY_0_2_6: subjects who received 3 doses of MenABCWY vaccine at Visit Month 0, Visit Month 2 and Visit Month 6 in study V102_15, and will receive 1 dose of MenABCWY in the extension study;

- B_0_2: subjects who received 2 doses of rMenB+OMV vaccine at Visit Month 0 and Visit Month 2 in study V102_15, and will receive 1 dose of rMenB+OMV in the extension study;
- ABCWY_ 0_6: subjects who received 2 doses of MenABCWY vaccine at Visit Month 0 and Visit Month 6 in study V102_15, and will receive 1 dose of MenABCWY in the extension study;
- Naive: approximately 200 subjects who are meningococcal vaccine-naive and of similar age to subjects enrolled from the parent study, and will receive either 2 doses of MenABCWY or rMenB+OMV in the extension study.

Table 3.1-1: Study Groups/planned sample size in V102_15E1

V102_15 (Primary Study)		**V102_15E1 ~24 months after last meningococcal vaccination in parent study**	
Group	**Vaccine (schedule)**	**Group**	**Number of Subjects***
ABCWY_0_2	MenABCWY (0, 2 months)	ABCWY_0_2	up to 196
ABCWY_0_2_6	MenABCWY (0, 2, 6 months)	ABCWY_0_2_6	up to 130
B_0_2	rMenB+OMV (0, 2 months)	B_0_2	up to 196
ABCWY_0_6	MenABCWY (0, 6 months)	ABCWY_0_6	up to 130
		Naive (freshly enrolled)	200

*Maximum enrolment derived from planned enrolment per group in parent trial

(Amended 4 April 2018)

Table 3.1-2: V102_15E1 Blood Draw and Vaccination Schedule for follow-on subjects

Group	Target enrolment	Day 1		Day 6	Day 16	Day 31		Day 91	Day 181
		Blood Draw	Vaccination	Blood Draw		Blood Draw			
ABCWY_0_2	100	20 mL	MenABCWY	20 mL	Safety Phone call	20 mL	Safety Evaluation	Phone Call for Safety Assessment	Phone Call for Safety Assessment and Study Termination
B_0_2	100	20 mL	rMenB+OMV	20 mL		20 mL			
ABCWY_0_2_6	100	20 mL	MenABCWY	20 mL		20 mL			
ABCWY_0_6	100	20 mL	MenABCWY	20 mL		20 mL			

Table 3.1-3: V102_15E1 Blood Draw and Vaccination Schedule for Naive subjects

	N	Day 1		Day 16	Day 31	Day 61	Day 66	Day 76	Day 91		Day 151	Day 241
		Blood Draw	Vaccination		Blood Draw	Vaccination	Blood Draw		Blood Draw			
Naive_ABCWY	100	20 mL	MenABCWY	Safety Phone call	20 mL	MenABCWY	20 mL	Safety Phone call	20 mL	Safety Evaluation	Phone Call for Safety Assessment	Phone Call for Safety Assessment and Study Termination
Naive_B	100	20 mL	rMenB+OMV		20 mL	rMenB+OMV	20 mL		20 mL			

Vaccination allocation: ***For naive subjects, interactive response technology (IRT) will randomly assign 1 dose of MenABCWY or rMenB+OMV, based on a 1:1 ratio. IRT will automatically schedule a second visit on Day 61 for naive subjects to receive a second dose of the same vaccine received on Day 1.***

No randomization to treatment arm for follow-on subjects is required as vaccine groups remain the same as in the parent study V102_15; however, vaccine allocation for follow-on groups will also be managed using IRT.

Block randomization will be used and within each block the treatments will be balanced.

Blinding: This is an open-label study.

Data collection: electronic Case Reporting Form (eCRF).

Study visits:

Follow on subjects: total of 3 clinic visits at Day 1, Day 6 and Day 31.

Naive subjects: total of 5 clinic visits at Day 1, Day 31, Day 61, Day 66 and Day 91.

Safety phone calls: Three safety phone calls (at Day 16, 91 and 181 for the follow on subjects and at Day 16, 76, 151 and 241 for the naive subjects) to collect medically-attended AEs, AEs leading to study withdrawal, SAEs and related medications and vaccinations.

(Amended 4 April 2018)

Written informed consent will be obtained from the subjects or from the parent or guardian according to the local regulations and GCP of the subject before conducting any study-specific procedures.

After signing informed consent, undergoing review of medical history, physical examination, prior medications/vaccination review, and confirmation of subject eligibility, subjects will be enrolled into the study.

Vaccination procedures: for the follow on subjects one IM injection on Visit Day 1 for the naive subjects two IM injections on Visits Day 1 and Day 61; one dose of the study vaccine will be administered each visit in the deltoid area of non-dominant arm for the naive subjects.

Post-vaccination evaluation:

Safety assessments of the subjects after vaccination will include:

- An observation period at the clinic for at least 30 minutes after each study vaccination. At 30 minutes post-vaccination, solicited local and systemic AEs, any unsolicited AE and body temperature will be recorded in source documents and eCRF.
- Solicited AEs occurring at the day of each study vaccination and the following 6 days (6 hours post vaccination to Day 7) will be recorded daily using an electronic Diary (eDiary). The eDiary will incorporate instructions on how to assess reactogenicity grades and what data to be entered. The subject will be provided with a user guide to support use of the system.
- Unsolicited AEs occurring within 30 days (Day 1 to Day 31) after each study vaccination will be collected by a safety phone call 15 days after the vaccination and at the clinic visit 30 days after the vaccination by interviewing the subject and/or subjects' parents / guardian (as applicable) and by review of available medical records.

- Medically-attended AEs, AEs leading to study withdrawal and SAEs will be collected during the entire study period. These data will be captured by interviewing the subject and/or subjects' parents / guardian (as applicable) during the site visits and phone calls and by review of available medical records. Subjects and/or parents / guardian will be encouraged to call the site in case of any medically-attended AEs or any AEs which they perceive as being of concern during the entire study period. 6 months after the last vaccination the subjects and/or parents / guardian will be contacted by the site to collect any safety related information.

Immunogenicity assessments of the subjects will include:

- Blood sample schedule: 3 samples for follow-on subjects– 20 mL at Day 1, Day 6 (for follow-on) and Day 31. For naive subjects 4 samples of 20 ml each will be collected – at Day 1, Day 31, Day 66 and Day 91. All samples will be collected prior to vaccination.

Interim Analysis:

None planned. Data for all primary and secondary objectives will be analyzed and reported in a final CSR after primary testing and analysis are completed. Analysis of the exploratory objectives may be completed after primary analysis and the data reported in an addendum, depending on time of completion of serological testing for these objectives.

3.2 Study Period

Each follow on subject should expect to participate in the study for approximately 6 months and each naive subject should expect to participate in the study for approximately 8 months, from the time of enrolment through the last study contact (6 months safety follow up phone call).

3.3 Blinding Procedures

There are no blinding procedures to be followed, as study is open-label.

3.4 Data Collection

3.4.1 Data Collected from Subjects

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

- Demographic Information.

- Adverse Events.
- Medical History.
- Concomitant Medications.

All data collected must only be identified using the GSK Subject ID, as described in section 5.1.4 Randomization.

3.4.2 Tools Used for Data Collection

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

3.4.2.1 Subject eDiary

Electronic Diaries (eDiaries) (refer to the eDiary Implementation and Compliance Summary for details), hereafter referred to as Subject eDiaries will be the only source document allowed for solicited local and systemic adverse events (including body temperature measurements), starting after the initial 30 minute***s*** post-vaccination period at the clinic till ***D***ay 7 after the vaccination (or until resolution, in case of solicited AEs ongoing after ***D***ay 7). The following additional rules apply to documentation of safety information collected in the Subject eDiary.

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

1. No corrections or additions data recorded by the subject *or* parent*(*s*)*/legal guardian*(*s*)* will be allowed once diary completion for that day has been performed.
2. The Subject eDiary will be designed in such a way as to prevent any blank, incomplete or biologically implausible entries. Subjects *or* parent*(*s*)*/legal guardian*(*s*)* will be instructed to fully complete the Subject eDiary each day, as per the instructions provided.
3. At or just in advance of each subject visit, site staff must review the eDiary data via the provider's web portal. It is necessary for site staff to acknowledge in the source documents that review of eDiary data for the preceding post-vaccination period has been performed. At the end of the study it is necessary for the investigator to acknowledge in the eCRF that the review of eDiary data has been performed for each subject. **"**For vaccination visits, site staff must ensure that each subject's Diary is prepared for data capture in the ensuing post-vaccination period by confirming the visit within the eDiary/eDiary system.

4. Any new safety information reported during the site visit (including a solicited reaction) cannot be entered into the Subject eDiary. Such information must be described in the source notes as a verbally-reported event. Any adverse reaction reported in this fashion must be described as an unsolicited reaction and therefore entered on the adverse event page of the eCRF.

(Amended 4 April 2018)

Case Report Forms

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

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

3.5 Collection of Clinical Specimens

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

- Blood.
- Urine (for females of childbearing potential only).

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

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

3.5.1 Blood Specimens

A sample of approximately 20 mL sample of blood will be drawn from all follow on subjects at visits Day 1 before vaccination, and at visits Day 6 and ***D***ay 31 and from all naive subjects at Visit Day1 before the vaccination and at visits Day 31, Day 66 and Day 91. The blood volume will not exceed 20 mL at each time point. A volume of 20 mL is

required in order to provide the necessary serum volume (approximately half of the blood draw volume) for the planned serology assays.

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

The total amount of blood collected over the study period per subject will be approximately 60 mL for follow-on subjects and 80 mL for naive subjects.

In order to minimize pain an anesthetic cream or patch (e.g. EMLA adhesives or cream) may be used at the site of blood sample draw, according to local practice. Not more than two attempts should be made to draw the required volume of blood.

The blood will be processed according to the Clinical Specimen Lab Manual and the serum will be distributed in aliquots using the tubes provided. All the aliquots will be stored at a temperature of ***-18***°C or ***below***. Each serum tube will be labeled with the labels provided by GSK. Serum samples will be sent to the sponsor or will be collected by a representative of the sponsor.

Complete instructions for labeling and storage of serum samples are included in the Clinical Specimen Lab Manual, which is stored in the investigator site file.

Testing of samples will be performed at GSK, Clinical Laboratory Sciences, Marburg, Germany or a delegate laboratory.

Samples will be retained in accordance with regulatory guidance for retention of essential study documents as described in section 10.

(Amended 4 April 2018)

3.5.2 Urine Specimens

Urine will be collected for pregnancy testing in females of child bearing potential. Urine will be collected at visit Day 1 (all) and ***D***ay 61 (naive) before vaccination, and the results recorded in the source document and eCRF.

(Amended 4 April 2018)

3.6 Stopping/Pausing Guidelines

There are no predetermined stopping rules other than circumstances for which subjects may not be eligible for additional study vaccinations as described in section 4. , Selection

of Study Population or may be withdrawn from the study according to the best interests of the subject as described in section 3.8 , Premature Withdrawal from Study.

3.7 Data Monitoring Committee

No Data Monitoring Committee will be convened for this study.

3.8 Premature Withdrawal from Study

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

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

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

3.8.1 Adverse Event

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

Subjects who develop a serious adverse event (SAE) judged to be possibly or probably related to the study vaccine, including hypersensitivity reactions, should not receive subsequent vaccination.

3.8.2 Death

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

3.8.3 Withdrawal of consent

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

3.8.4 Lost to Follow-Up

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

3.8.5 Administrative Reason

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

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

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

Subject Compliance: Subjects should submit diary data each day for the first 7 days after each vaccination. Subject must be contacted by phone if they fail to submit data on 2 or more days during the first 7 days after each vaccination.

3.8.6 Protocol Deviation

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

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

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

3.9 End of Study

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

A subject is considered to have completed the study when he/she has completed the last study visit/contact (Follow on subjects at Day 181 and the naive subjects at ***D***ay 241) and provided safety information.

For the purpose of this protocol, the end of study is defined as the date of the last testing/reading released of human biological samples or imaging data, related to primary and secondary end points, to be achieved no later than 8 months after Last Subject Last Visit (LSLV).

(Amended 4 April 2018)

4. SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

Follow-on Participants

- Subjects from Finland and Poland previously enrolled in study V102_15 who have received all planned meningococcal vaccinations in the study[1]
- Who have not received any additional meningococcal vaccination since the last meningococcal vaccination administered in the parent trial.
- Who have given written informed consent or assent (as applicable) after the nature of the study has been explained according to local regulatory requirements, prior to study entry. If the subject is under age 18 at the time of enrollment, the parent(s)/ legal guardian(s) of the subject should have given their written consent.
- Individuals of who the investigator believes can and will comply with the requirements of the protocol (e.g. use of an eDiary, return for follow-up visits, available for phone contacts).
- Individuals in good health as determined by the outcome of medical history, physical examination and clinical judgment of the investigator.

Naive Group

- Male and female individuals of similar age (approximately 12-20 years) to follow-on subjects from V102_15 trial.
- Who have not received any meningococcal vaccination since birth
- Individuals who have given their written informed consent or assent (as applicable) after the nature of the study has been explained according to local regulatory requirements, prior to study entry. If the subject is under age 18 at the time of enrollment, the parent(s)/ legal guardian(s) of the subject should have given their written consent.
- Individuals of who the investigator believes can and will comply with the requirements of the protocol (e.g. use of an eDiary, return for follow-up visits, available for phone contacts).

[1] Subjects will be eligible if they have received meningococcal vaccinations according to randomization assignment, irrespective of protocol-specified window.

- Individuals in good health as determined by the outcome of medical history, physical examination and clinical judgment of the investigator.

4.2 Exclusion Criteria

Follow-on Participants:

Follow-on individuals not eligible to be enrolled in the study are those with:

- History of any meningococcal vaccine administration since last meningococcal vaccination administered in V102_15 parent study.
- Current or previous, confirmed or suspected disease caused by *N. meningitidis*, since termination from parent study.
- Household contact with and/or intimate exposure to an individual with any laboratory confirmed *N. meningitidis* infection within 60 days of enrollment.
- If the subject is female of childbearing potential, sexually active, and has not used any of the acceptable contraceptive methods[1] for at least 2 months prior to study entry and for the duration of the trial.
- Pregnancy or breast-feeding .
- History of severe allergic reactions after previous vaccinations or hypersensitivity to any vaccine component including diphtheria toxoid (CRM197) and latex.
- Progressive, unstable or uncontrolled clinical conditions.
- Any confirmed or suspected condition with impaired/altered function of immune system (immunodeficient or autoimmune conditions).
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within three months prior to the study vaccination or planned use throughout the study period. (For corticosteroids, this means prednisone, or equivalent, ≥ 20 mg/day. Inhaled, intranasal and topical steroids are allowed).

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

- Administration of blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation in the 3 months prior to study enrolment.
- Received an investigational or non-registered medicinal product within 30 days prior to informed consent.
- Administration of any vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to enrollment in the study, or within 7 days after vaccination in the study. (See section 4.3 for additional details).
- Clinical conditions representing a contraindication to intramuscular vaccination and/or blood draws.
- Who have received systemic antibiotic treatment within 3 days prior to any blood draw.
- Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the subject due to participation in the study.

Naive Individuals

Naive individuals not eligible to be enrolled in the study are those with:

- History of any meningococcal vaccine administration since birth.
- Current or previous, confirmed or suspected disease caused by *N. meningitidis*.
- Household contact with and/or intimate exposure to an individual with any laboratory confirmed *N. meningitidis* infection within 60 days of enrollment.
- If the subject is female of childbearing potential, sexually active, and has not used any of the acceptable contraceptive methods[1] for at least 2 months prior to study entry and for the duration of the trial.
- Pregnancy or breast-feeding.

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

- History of severe allergic reactions after previous vaccinations or hypersensitivity to any vaccine component including diphtheria toxoid (CRM197) and latex.
- Progressive, unstable or uncontrolled clinical conditions.
- Any confirmed or suspected condition with impaired/altered function of immune system (immunodeficient or autoimmune conditions).
- Chronic administration (defined as more than 5 days) of immunosuppressants or other immune-modifying drugs within 30 days prior to the study enrolment. (For corticosteroids, this means prednisone, or equivalent, ≥ 20 mg/kg/day. Inhaled, intranasal and topical steroids are allowed).
- Administration of blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation in the past 3 months or planned use throughout the study period.
- Received an investigational or non-registered medicinal product within 30 days prior to informed consent.
- Individuals who are part of study personnel or close family members conducting this study.
- Administration of any vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to enrollment in the study, or within 7 days after first vaccination, and/or planned use of any vaccine 7 days prior to and 7 days after second vaccination. (See section 4.3 for additional details)
- Clinical conditions representing a contraindication to intramuscular vaccination and/or blood draws.
- Who have received systemic antibiotic treatment within 3 days prior to any blood draw.
    - Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the subject due to participation in the study.

4.3 Criteria for Delay of Vaccination

After enrollment, subjects may encounter clinical circumstances that warrant a delay in subsequent study vaccination. These situations are listed below. In the event that a subject meets a criterion for delay of vaccination, the subject may receive study vaccination once the window for delay has passed as long as the subject is otherwise eligible for study participation.

- Acute moderate or severe infection with or without fever within 3 days of intended study vaccination.
- Fever is defined as body temperature ≥38.0° C within 3 days of intended study vaccination.
- Administration of any vaccine not foreseen by the study protocol within 14 days prior to first vaccination and, if applicable, 7 days prior to the second study vaccination.

Prior to receipt of repeat study vaccination, subjects must be evaluated to confirm that they are eligible for subsequent vaccination. If subjects meet any of the criteria listed below, they should not receive additional vaccinations:

- Subjects who experienced any immediate allergic reaction after the previous study vaccination.
- Subjects who experience any serious adverse event judged to be possibly or probably related to study vaccination, including hypersensitivity reactions.
- Subjects who develop any clinically significant medical condition which, in the opinion of the investigator, may pose additional risk to the subject if he/she continues to participate in the study.
- Subjects who are pregnant.

Subjects who meet any of these criteria must not receive further study vaccinations. However, these subjects should be encouraged to continue study participation, as discussed in section 3.7 .

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

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

Under such circumstances, a subject may be considered eligible for study enrolment after the appropriate window for delay has passed and inclusion/exclusion criteria have been rechecked, and if the subject is confirmed to be eligible.

5. STUDY PROCEDURES

The sections that follow provide an overview of the procedures that are to be followed in enrolling, evaluating, and following subjects who participate in this clinical study. Visits can be either clinic visits or safety follow-up telephone calls, as specified in the Table below and in the Time and Events Table 5 and 6

Table 5-1: Study Procedures

Visit Category	Procedures
Pre-vaccination Clinic Visit(s)	Section 5.1 describes procedures to be followed prior to study vaccination: informed consent/assent, screening, enrolment, and randomization Note; Randomization / vaccine allocation in IRT must occur immediately before giving vaccine to subject. If pre-vaccination clinic visit does not happen on the same day as vaccine administration, randomization / vaccine allocation in IRT be performed only on the day of vaccination
Vaccination Clinic Visit(s)	Section 5.2 describes procedures to be followed during each clinic visit involving vaccination: vaccination, post-vaccination procedures, and post-vaccination reminders
Post-vaccination Visit(s)	Section 5.3 describes follow-up clinic visits and safety follow-up calls
Unscheduled Visit(s)	Section 5.4 describes possible procedures to be followed at unscheduled clinic visit
Study Termination Visit	Section 5.5 describes procedures to be followed at the last study visit for a subject (may include early termination visit)

5.1 Pre-vaccination Clinic Visit(s)

This section describes the procedures that must be performed for each potential subject prior to vaccination, including obtaining informed consent/assent, screening, enrolment and randomization. All procedures listed in sections 5.1.1 and 5.1.2 can be performed up to 7 days prior to enrolment on Day 1.

Procedures listed in sections 5.1.3 and 5.1.4 must be performed on the same day as vaccination.

5.1.1 Informed Consent/Assent

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

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

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

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

If at any point in the trial after Day 1, subject has reached the age when the individual informed consent must be given in addition to the provided assent form, the subject's informed consent has to be obtained prior to any study-specific procedures.

5.1.2 Screening

After an individual or individual's parent/guardian has consented to participate in the study and informed consent/assent has been signed, that individual will be given a unique sequential Screening Number by the investigator. The subject's unique Screening Number will be documented in the Screening and Enrolment log. The eligibility of the subject will be determined based on the inclusion and exclusion criteria listed in section 4. , Selection of Study Population and evaluated during this screening procedure.

Prior to study enrolment, demographic data will be collected from the subject, including date of birth, gender, race, and ethnicity.

Medical history will also be collected, including but not limited to any medical history that may be relevant to subject eligibility for study participation such as prior vaccinations, concomitant medications, and previous and ongoing illnesses or injuries. Relevant medical history can also include any medical history that contributes to the understanding of an adverse event that occurs during study participation, if it represents an exacerbation of an underlying disease/pre-existing problem. Medical history will be collected from birth for naive subjects and from end of participation in study V102_15 for follow-on subjects.

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

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

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

Perform pregnancy testing in women of childbearing age (refer to section 3.5 , for guidance regarding the procedure).

A general physical examination is to be performed by a qualified health care practitioner. "Qualified health care practitioner" refers to any licensed health care professional who is

permitted by institutional policy to perform physical examinations and who is identified within the Study Staff Signature Log.

These data will be written in the source document (see section 9.1 Source Documentation).

In the event that the individual is determined ineligible for study participation, he/she is considered a screen failure. The reason for screen failure must be documented in the Screening and Enrolment log. If the individual is determined to be eligible for the study, he/she will be enrolled into the study.

5.1.3 Enrolment

After the signed informed consent form has been obtained and an individual is determined to be eligible for study participation, the subjects will be enrolled using Interactive Response Technology (IRT) system. For follow-on subjects, the same Subject ID that was assigned in the parent study will be used for the extension trial. For naive subjects, a new Unique Subject ID will be assigned in IRT. The Subject ID number consists of a 7 digit number resulting from the combination of the site number and the subject's order of randomization at the site. Access to IRT can be obtained by the site staff either via web or telephone (as back up).

As soon as the target number (upper limit) of naive subjects in each vaccine (MenABCWY or MenB) group has been reached, the enrollment will be frozen. Additional subjects may be enrolled into the study at the discretion of the sponsor in the case of any subject who was randomized but did not receive any study vaccine.

5.1.4 Randomization

Enrolled naive subjects will be randomized in the IRT system and automatically assigned a unique Subject ID. Enrolled follow-on subjects will be assigned the same Subject ID that was used in the parent trial. The Subject ID assigned by IRT will be the subject's unique identification number for all eCRFs and associated study documentation that will be used for duration of the study. After randomization, the Screening Number ceases to be used and remains in the Screening and Enrolment Log only. The list of randomization assignments is produced by the IRT service provider and approved by GSK Randomization Office according to applicable GSK Standard Operating Procedure (SOP).

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

document as specified in the Source Data Agreement (SDA). The information on subjects who are randomization failures should be kept distinct from subjects who are screen failures, as described in section 5.1.2 , Screening.

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

For follow on subjects, on Visit ***D***ay 1, IRT will assign a pack ID of the same treatment received in the V102_15 (MenABCWY or rMenB+OMV).

For Naive subjects, IRT will randomly assign 1 dose of MenABCWY or rMenB+OMV, based on a 1:1 ratio. IRT will automatically schedule a second visit on Day 61 for naive subjects to receive a second dose of the same vaccine received on ***D***ay 1.

(Amended 4 April 2018)

5.2 Vaccination Clinic Visit(s)

The first vaccination will be performed on ***D***ay 1 for all subjects. The naive subjects will receive their second dose at Day 61 visit.

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

Ensure all serology samples are taken prior to each vaccination, if applicable. Refer to section 3.5 for further detail regarding the sample volume and general handling of blood sample.

After completing the pre-vaccination procedures on ***D***ay 1 for all subjects and at Day 61 for naive subjects, administer the vaccine to the subject according to the procedures described in section 6.3 , Vaccine Preparation and Administration.

Prior to administration of each vaccination at visit Month 1, Month 2, Month 6 and Month 12, confirm that the subject is eligible for additional study vaccination and does not meet any criteria for delaying additional study vaccinations as described in section 4. , Selection of Study Population.

<u>Pre-vaccination procedures at Visits Day 1 for all subjects and at Day 61 for the naive subjects, Month 2, Month 6 and Month 12</u>

- A general physical examination is to be performed by a qualified health care practitioner. "Qualified health care practitioner" refers to any licensed health care professional who is permitted by institutional policy to perform physical examinations and who is identified within the Study Staff Signature Log.
- Perform pregnancy test in all female subjects of childbearing potential (refer to section 3.5 for guidance regarding the procedure).
- Ensure all serology samples are taken **prior** to each vaccination, as applicable (all subjects at Day 1).
- Use IRT system to assign a Pack Number containing the treatment to be administered to the naive and follow on subjects. IRT will assign a treatment according to a randomization list to naive subjects. IRT will assign to follow on subjects the vaccination (MenABCWY or MenB) they received in the V102_15 study. Each Pack Number, actually administered to the subject, must be recorded in the eCRF.

After completing the pre-vaccination procedures at Visit Day 1 and Day 61 for the naive subjects, administer the vaccine to the subject according to the procedures described in section 6.3 , Vaccine Preparation and Administration.

(Amended 4 April 2018)

5.2.1 Post-vaccination Procedures

The following post-vaccination procedures will be performed on ***D***ay 1 for all subjects and at ***D***ay 61 for the naive.

After vaccination, the subject will be observed for at least 30 minutes including observation for unsolicited adverse events, solicited adverse events, and body temperature measurement. Record all safety data collected during this time in the subject's source document.

A Subject eDiary will be used in this study to document solicited adverse events. The Subject eDiary is the only source for collection of these data; therefore, it is critical that the subject completes the Subject eDiary correctly. The subject should be trained on how and when to complete each field of the Subject eDiary.

The subject or parent(s)/legal guardian(s) should be trained on how to self-measure local solicited adverse events and body temperature. The measurement of solicited local adverse events is to be performed using the ruler provided by the site.

The subject or parent(s)/legal guardian(s) should be instructed how to perform body temperature measurement using the thermometer provided by the site. If the subject feels

unusually hot or cold during the day, the subject or parent(s)/legal guardian(s) should check body temperature. If the subject has fever, the highest body temperature observed that day should be recorded in the Subject eDiary.

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

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

Subject eDiary assignment and use:

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

Subject eDiary instructions must ensure that the subject or parent(s)/legal guardian(s) understands the following:

- Timely completion of the Subject eDiary on a daily basis is a critical component to study participation.
- The Subject eDiary will allow certain time windows for completion of each day's observations.
- The Subject eDiary employs the use of audio-visual alarms to ensure timely completion of data entry.
- The trained and assigned user of the Subject eDiary must not share access codes with anyone.

- A helpdesk will be provisioned for them in case of technical issues, though it must be stressed that the Helpdesk is not a replacement for normal medical care and no medical issues can be discussed with the agents.
- The Subject eDiary itself must never be considered a substitute for direct medical care and any concerns must be communicated to site staff as soon as possible.

The site should schedule the next study activity clinic visit or safety follow-up call with the subject or parent(s)/legal guardian(s).

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

(Amended 4 April 2018)

5.2.2 Post-vaccination Reminders

No post-vaccination reminder calls will be performed in the study.

The subject or parent(s)/legal guardian(s) will receive daily reminders via the Subject eDiary device's in-built audio-visual alarms to alert the user to complete the diary during the post vaccination period. From Day 1 though Day ~~8~~*7*, or until resolution of the last reported solicited AE, the users will receive daily alerts through the Subject eDiary to record the incidence of any potential unsolicited AEs, and whether these AEs were medically attended (defined as symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a health care provider), or were of concern. In case of such events, subjects/parents will be instructed to contact the site as soon as possible to report the event(s).

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

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

Sites must assess these alerts when received and contact subjects as necessary. Please refer to section 3.8 , Premature Withdrawal from Study and section 7.1.3 , Evaluation of Adverse Events for guidance on necessary action in the event of one of these alerts.

Unsolicited Adverse Event Safety Follow Up Calls

The site will call the subjects or parent(s)/legal guardian(s) 15 days after the vaccination to collect/observe any safety concerns (unsolicited AEs, SAEs, and medically attended AEs).

5.3 Post-vaccination Visit(s)

Post-vaccination visits will be performed on:

Follow on subjects: 5 days after the vaccination to collect the blood sample, 30 days after the vaccination to evaluate the subject's safety and to collect the blood sample.

Naive subjects: 30 days after the first vaccination to collect a blood sample and evaluate the subject's safety and 5 days after the second vaccination (Day 66) to collect the blood sample and 30 days (***D***ay 91) after the second vaccination to evaluate the subject's safety and to collect the blood sample.

5.3.1 Follow-up Clinic Visit(s)

Safety follow-up clinic visits will be performed on ***D***ay 31 after each vaccination (follow on subjects at Day 31 and the naive subjects at ***D***ay 31 and ***D***ay 91).

During the follow-up clinic visit, the Subject eDiary will be reviewed. No changes to the information recorded within the Subject eDiary are permissible. For details on the Subject eDiary see sections 3.4.2 , Tools Used for Data Collection and 5.2.1 Post-vaccination Procedures. The subject or parent(s)/legal guardian(s) will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken/received in the time since the last clinic visit. This interview will follow a script which will facilitate the collection of relevant safety information. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. Adverse events reported by the subject or parent(s)/legal guardian(s) at this follow-up clinic visit must be recorded in the subject's source document and on an Adverse Events eCRF, as specified in section 7.1 , Safety Assessment, and not written on the script used for the interview.

Perform a brief symptom-directed physical examination if necessary according to symptoms the subject has reported. This is a physical examination that will include an

examination of organ systems that are relevant to the investigator based on review of the subject's reported adverse events, concomitant medication use This assessment may include: measurement of vital signs, body temperature (specify route) and a check of general appearance. Measure the subject's height and weight. The physical assessment must be performed by the investigator or designee of the investigator, who is qualified to perform a physical assessment in accordance with their institutional policy. Corresponding information is documented in the subject's source document and eCRF(s).

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

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

(Amended 4 April 2018)

5.3.2 Safety Follow-up Calls

Safety follow-up calls will be performed on Day 16 after each vaccination (all subjects at ***D***ay 16 and the naive subjects at ***D***ay 76). At least 3 attempts should be made to reach the subject or subjects's parent/legal guardian.

Safety follow-up calls are calls made to the subject or subject's parent/legal guardian 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 or parent(s)/legal guardian(s) will be interviewed according to the script, and information relating to unsolicited adverse events (AEs), serious adverse events (SAEs), medically attended adverse events, 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 activity (clinic visit) with the subject or parent(s)/legal guardian(s).

The subject and/or parent(s)/legal guardian(s) will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

(Amended 4 April 2018)

5.4 Unscheduled Visits

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

5.5 Study Termination Visit

The planned study termination visit will occur on ***D***ay 181 for the follow on subjects and at ***D***ay 241 for the naive subjects (6 months after the last vaccination), and will be performed by telephone call. However, in case of early terminations, the termination visit may be a clinic visit or a telephone call. The date of termination is the date of the last contact (clinic visit or telephone call) in which the subject's health status was assessed or, in cases where the subject does not agree to any further safety follow-up, it is the date consent is withdrawn. This date should be recorded on the termination eCRF page. For visit procedures to be performed for a subject whose planned study participation ends prematurely, please see section 5.5.1 , Early Termination Visit.

During the telephone call (at ***D***ay 181 for the follow on subjects and ***D***ay 241 for the naive subjects), the following procedures will be performed: Collect medically-attended AEs, SAEs, and concomitant medications for these events.

The site will review with the subject and/or parent(s)/legal guardian(s) the plan of when information relating to the subject's participation in the study may be available (e.g., study results, treatment assignments). It will also be discussed how information relating to the subject's participation in the study will be shared with the subject's healthcare provider, if the subject and/or parent(s)/legal guardian(s***)*** chooses to share this information.

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

(Amended 4 April 2018)

5.5.1 Early Termination Visit

When a subject is withdrawn from treatment or withdraws from the study, the investigator will notify the Sponsor and, when possible, will perform the procedures listed below. The reason(s) for the early termination will be included in the subject's source documentation. If the Early Termination Visit is a telephone call, collect as much information as possible. Early Termination Visits include subjects who were randomized but not treated.

At the clinic visit or during the telephone call, the following procedures will be performed:

The date of termination from the study is the date of the last contact (clinic visit or telephone call) in which the subject's health status was assessed or, in cases where the subject does not agree to any further safety follow-up, it is the date consent is withdrawn. This date should be recorded on the termination eCRF page.

When a subject is withdrawn from treatment or withdraws from the study, the investigator will notify the Sponsor and, when possible, will perform the procedures listed below. The reason(s) for the early termination will be included in the subject's source documentation. If the Early Termination Visit is a telephone call, collect as much information as possible. Early Termination Visits include subjects who were randomized but not vaccinated.

At the clinic visit or during the telephone call, the following procedures will be performed:

- review solicited AEs collected using eDiary (if applicable) and collect the eDiary device (or schedule a contact to return device to the site, if applicable);
- interview of subject / subject's parent/legal guardian to collect unsolicited adverse events (if applicable for the study period), medically attended adverse events, AEs leading to withdrawal from the study and SAEs;
- interview of subject / subject's parent/legal guardian to collect concomitant medications/ vaccinations;
- perform symptom-directed physical assessment including any organ system warranting further examination based on reporting AEs (if applicable);
- collect blood sampling for immunogenicity assessment (if requested by the protocol at the time of the study termination).

The site will review with the subject and/or parent/legal guardian the plan of when information relating to the subject's participation in the study may be available (e.g., study results, treatment assignments). It will also be discussed how information relating to the subject's participation in the study will be shared with the subject's healthcare provider, if the subject and/or parent/legal guardian chooses to share this information.

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

The site will review with the subject and/or parent(s)/legal guardian(s) the plan of when information relating to the subject's participation in the study may be available (e.g., study results, treatment assignments). It will also be discussed how information relating to the subject's participation in the study will be shared with the subject's healthcare

provider, if the subject and/or parent(s)/legal guardian(s) chooses to share this information.

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

6. TREATMENT OF SUBJECTS

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

6.1 Study Vaccine(s)

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

GSK Meningococcal ABCWY Vaccine (MenABCWY): Fixed-combination vaccine obtained by reconstitution and extemporaneous mixing of lyophilized MenACWY powder with liquid rMenB + OMV suspension for injection in deltoid muscle. The total volume for injection is ≥ 0.5mL of solution.

GSK Meningococcal B Recombinant vaccine (rMenB+OMV): Each dose contains histidine buffer solution, NaCl and sucrose as excipients and aluminum hydroxide as adjuvant. The rMenB containing components are presented as 0.6 mL monodose preparations in pre-filled, 1 mL colorless (Type I, Ph. Eur.) syringes. Vaccine supplied as a single 0.5 mL injectable dose administered IM into the deltoid area according to the relevant EU and US Summary of Product Characteristics.

Table 6.1-1: Composition of MenABCWY: Lyophilized Men ACWY reconstituted with one dose of rMenB (+OMV) (1 dose =0.5mL).

Name of Ingredient	Unit and/or Percentage Formula (Dose 0.5 mL)
Drug Substances	
MenA-CRM_{197} conjugate	10 µg MenA oligosaccharide
MenC- CRM_{197} conjugate	5 µg MenC oligosaccharide
MenW- CRM_{197} conjugate	5 µg MenW oligosaccharide
MenY- CRM_{197} conjugate	5 µg MenY oligosaccharide
Recombinant Neisseria meningitis Protein 287-953	50 µg*
Recombinant Neisseria meningitis Protein 961c	50 µg*
Recombinant Neisseria meningitis Protein 936-741	50 µg*
OMV from *N meningitidis* Strain NZ 98/254	25 µg*
Excipients and Adjuvant	
Potassium dihydrogen phosphate	0.45-0.62 mg***
Sucrose	22.5 mg ****
Sodium chloride	3.12 mg
Histidine	0.776 mg
Al(OH)3	1.5 mg**
Water for Injections	Q.s. to 0.5 mL

*Total amount of protein concentration is calculated individually for each protein. The target concentrations are met according to bulks' concentration values, which are determined by bicinchoninic Acid (BCA) protein assay.

**Aluminium Hydroxide: 1.5 mg corresponds to 0.5 mg of elemental Aluminium.

*** the effective quantity of Potassium dihydrogen phosphate comes from the amount of rMenB(+OMV) vaccine and the quantity present in the MenACWY lyophilized;

**** resulting from the contribution of MenACWY lyophilized (2.5%) re-suspended with one dose of rMenB (+OMV) (2.0%).

rMenB+OMV (Bexsero):

One dose (0.5 ml) contains:

- Recombinant *Neisseria meningitidis* group B NHBA fusion protein[1,2,3] (50µg);
- Recombinant *Neisseria meningitidis* group B NadA protein[1,2,3] (50µg);
- Recombinant *Neisseria meningitidis* group B fHbp fusion protein[4,5,6] (50µg);
- Outer membrane vesicles (OMV) from *Neisseria meningitidis* group B strain NZ98/254 measured as amount of total protein containing the PorA P1.4 [2] (25µg).

6.2 Non-Study Vaccines

Not applicable

6.3 Vaccine Preparation and Administration

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

The study vaccine should be allowed to reach room temperature before administration according to local vaccination practice.
Final MenABCWY combined vaccine is generated by aseptically injecting the whole content of one prefilled syringe of rMenB+OMV into the vial containing the lyophilized MenACWY component. This reconstitutes the lyophilized MenACWY component with gentle agitation. The final mixed vaccine (total volume approximately 0.6 mL; injection volume 0.5 ml) is then ready for administration of the MenABCWY formulation.
The rMen+OMV vaccine must be prepared according to the package insert / Summary of Product Characteristics.

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[1] produced in *E. coli* cells by recombinant DNA technology.

[2] adsorbed on aluminium hydroxide (0.5 mg Al^{3+}).

[3] NHBA (Neisseria Heparin Binding Antigen), NadA (Neisserial adhesin A), fHbp (factor H binding protein).

[4] produced in *E. coli* cells by recombinant DNA technology.

[5] adsorbed on aluminium hydroxide (0.5 mg Al^{3+}).

[6] NHBA (Neisseria Heparin Binding Antigen), NadA (Neisserial adhesin A), fHbp (factor H binding protein).

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

PRECAUTIONS TO BE OBSERVED IN ADMINISTERING STUDY VACCINE:

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

Eligibility for subsequent study vaccination is determined by following the criteria outlined in section 4.3 , Criteria for Delay of Vaccination.

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

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

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

6.4 Vaccine Administration Error or Overdose of Vaccine

Vaccine administration error is defined as receiving a dose of study vaccine that was not reconstituted as instructed or administered by a different route from the intended route of administration. An overdose of study vaccine (whether accidental or intentional) is defined when a dosage higher than the recommended dosage is administered in one dose of study vaccine (referred to Table 3.1-1).

An overdose would also occur if two doses of the study vaccine are administered within half the time of the recommended interval between doses, as defined in the protocol.

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

6.5 Prior and Concomitant Medications and Vaccines

Concomitant medications include (at a minimum) all prescription and nonprescription medications (with the exception of mineral supplements and vitamins) taken regularly by a subject at the time of study enrolment.

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

- Any investigational or non-registered product (drug or vaccine) received within 30 days prior to enrollment;
- Any vaccines administered within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to enrollment;
- Any immunosuppressants or other immune-modifying drugs including systemic steroids, within 3 months prior to enrolment;
- Any immunoglobulins or blood products within 3 months prior to enrolment;
- Any systemic antibiotics within 3 days prior to enrolment.

If these medications were administered to the subject within the specified window prior to the first study vaccination they must be recorded on the Prior and Concomitant Medications eCRF.

The use of antipyretics and/or analgesic medications within 24 hours prior to any study vaccination must be recorded in eCRF. The administration of antipyretics / analgesics within 7 days after study vaccination must be recorded and the reason for their use (prophylaxis versus treatment) must be collected.

Medications taken for prophylaxis are those administered in absence of any symptom and intended to prevent the onset of post-vaccination symptoms. Medications taken for treatment are intended to reduce or eliminate the symptoms that are present.

At each study visit/safety phone contact, the investigator will question the subject / subject's parents/guardian about any medication(s) and vaccination(s) given to the subject.

Any concomitant medications administered for treatment of AEs with medically-attended visit, AEs leading to study withdrawal and SAEs must be documented during the entire study period.

Any treatments and/or medications specifically contraindicated, e.g., any investigational or non-registered product, any immunosuppressants and immune-modifying drugs including systemic steroids, any immunoglobulins and blood products should be checked at each study visit / safety phone call subsequent to the study vaccination. If any became applicable during the study, it will not require withdrawal of the subject from the study but may determine a subject's evaluability in the per-protocol analysis. See section 8.3 for definition of study populations to be evaluated.

Any vaccine not foreseen in the study protocol in the period starting at Visit 1 and ending at Last visit must be recorded in the eCRF.

6.6 Vaccine Supply, Labeling, Storage and Tracking

The Sponsor will ensure the following:

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

The investigator must ensure the following:

- Acknowledge receipt of the study vaccines by a designated staff member at the site, including:
  - Confirmation that the vaccines were received in good condition.
  - Confirmation to the Sponsor of the temperature range during shipment from the Sponsor to the investigator's designated storage location.
  - Confirmation by the Sponsor that the vaccines are authorized for use.
- Proper storage of the study vaccines, including:
  - Storage in a secure, locked, temperature-controlled location.
  - Proper storage according to the instructions specified on the labels.
  - Appropriate record keeping and inventory of the study vaccines, including regular documentation of adequate storage temperature.
- Appropriate use of the study vaccines, including:
  - Not use of vaccines prior to receipt of authorization for use from the Sponsor.
  - Use only in accordance with the approved protocol.
  - Proper handling, including confirmation that the vaccine has not expired prior to administration.

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

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

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

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

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

7. ASSESSMENTS

7.1 Safety Assessment

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

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

The period of observation for AEs extends from the time the subject signs informed consent until he or she completes the final study visit (Visit Month 13) or terminates the study early (whichever comes first). AEs occurring after the informed consent form is signed but prior to receiving study vaccine/product will be documented as an adverse event and recorded within source document. However, any AEs occurring prior to receipt of any study vaccine will be analyzed separately from “treatment emergent” AEs (AEs occurring after administration of the first study vaccine).

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

7.1.1 Solicited Adverse Events

The term “reactogenicity” refers to solicited signs and symptoms (“solicited adverse events”) occurring in the hours and days following a vaccination, to be collected by the subject and/or parent(s)/legal guardian(s) for 7 consecutive days (6 hours – Day 7), using a pre-defined checklist in an eDiary.

The following solicited adverse events are included in the eDiary.

7.1.1.1 Solicited local adverse events:

Pain, erythema and induration**.**

Solicited systemic adverse events:

Fatigue, headache, myalgia, arthralgia, loss of appetite, nausea, chills, and fever (body temperature ≥38.0°C).

Each adverse event is to be assessed using the scoring system reported in Table 7.1.1-1:

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

	Mild	Moderate	Severe
Pain	***No interference with daily activity***	***Interferes with daily activity***	***Prevents daily activity***
Erythema	25-50mm	51-100mm	> 100 mm
Induration	25-50 mm	51-100 mm	> 100 mm
Fatigue	***No interference with daily activity***	***Interferes with daily activity***	***Prevents daily activity***
Headache	***No interference with daily activity***	***Interferes with daily activity***	***Prevents daily activity***
Myalgia	***No interference with daily activity***	***Interferes with daily activity***	***Prevents daily activity***
Arthralgia	***No interference with daily activity***	***Interferes with daily activity***	***Prevents daily activity***
Loss of appetite	***Eating less than usualwith no effect on normal activity***	***E~~e~~***ating less than usual/ interfered with normal activity	***N~~n~~***ot eating at all
Nausea	***No interference with daily activity***	***Interferes with daily activity***	***Prevents daily activity***
Chills	***N***o interference with activity	***Interferes with daily activity***	***P***revents daily activities

Fever is defined as body temperature ≥ 38.0°C. Preferable route of temperature measurement is oral.

Other indicators of reactogenicity:

- Use of analgesics / antipyretics for treatment;
- Use of analgesics / antipyretics for prophylaxis;
- Body temperature.

The study staff must review the data entered into the eDiary as described in section 3.4.2 , Tools Used for Data Collection and section 5.3.1 , Follow-up Clinic Visit(s).

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

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

7.1.2 Unsolicited Adverse Events

An unsolicited adverse event is an adverse event that was not solicited and that was spontaneously communicated by a subject and/or parent/legal guardian who has signed the informed consent.

7.1.3 Evaluation of Adverse Events

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

The severity of events reported on the Adverse Events 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.

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

1. Not Related

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

2. Possibly Related

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

3. Probably Related

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

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

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

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

- "Medically attended adverse event": an adverse event that leads to a visit to a healthcare provider.
- AEs leading to withdrawal: adverse events leading to study or vaccine withdrawal.

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

7.1.4 Serious Adverse Events

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

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

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

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

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

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

1. Related/suspected

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

2. Not Related

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

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

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

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

7.1.4.1 Adverse Events of Special Interest

Not applicable.

7.1.5 Methods for Recording Adverse Events and Serious Adverse Events

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

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

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

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

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

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

7.1.5.1 Post-Study Events

Any SAE that occurs outside of the protocol-specified follow-up period and considered to be caused by the study vaccine must be reported to GSK or its designee. These SAEs will be processed by GSK or its designee as during the course of the study, until 6 months after end of the study. Instructions and contact details for collecting and reporting these suspected SAEs will be provided to the investigator.

7.1.6 Pregnancies

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

Pregnancy data must be recorded on a Pregnancy Report eCRF (initial report) and Pregnancy Follow-Up eCRF (outcome report) and reported to GSK or delegate. Instructions and contact details for submitting the Pregnancy eCRFs will be provided to the investigator.

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

7.1.7 Safety Laboratory Measurements

This study has no safety laboratory measurements.

7.2 Efficacy Assessment

This study has no efficacy assessments.

7.3 Immunogenicity Assessment

The measures of immunogenicity used in this study are standard, i.e., widely used and generally recognized as reliable, accurate, and relevant (able to describe the quality and extent of the immune response). Testing will be conducted by a GSK or designated laboratory in a blinded manner towards the treatment arm and the visit.

The functional measure of immunogenicity used in this study, Serum Bactericidal Assay (SBA), is a measure of the ability of antibodies, mediated with complement, to kill meningococci, and is widely used and generally recognized as the serological correlate of protection. Human Serum Bactericidal Assay using human complement (hSBA) for *N.meningitidis* serogroups A, C, W, Y and serogroup B strains will be performed in GSK, Clinical Laboratory Sciences, Marburg (Germany) or in a qualified and certified laboratory designated by GSK using the identical standardized, validated procedures with adequate controls.

(Amended 4 April 2018)

7.3.1 HT-hSBA

The High Throughput human Serum Bactericidal Assay using human plasma as the source of exogenous complement (HT-hSBA) will be used to measure the induction of functional complement dependent bactericidal antibodies directed against meningococcal serogroups A, C, W and Y and serogroup B strains following the study vaccination. The key measures of immunogenicity will be the percentages of subjects with hSBA ≥ LLOQ, hSBA GMTs, and the percentage of subjects with four-fold titer rise against serogroups A, C, W and Y and serogroup B strains. A post-vaccination hSBA titer ≥4 is used as an accepted correlate of protection against invasive meningococcal disease (Goldschneider et al, 1969a; Goldschneider**,** et al 1969b). ***The sample testing schedule is summarized in Table 7.3-1.***

Table 7.3-1: Sample Testing Schedule in V102_15E1

Assay Type	Subject pool	V102_15E1 (extension study)				
		Day 1	Day 6	Day 31	Day 66	Day 91
HT-hSBA (all enrolled)	Follow-on	√	√	√		
	naive	√		√	√	√

HT-hSBA = high throughput human serum bactericidal assay

Serum bactericidal activity against *N. meningitidis* serogroup B strains will be determined by performing HT hSBA against four meningococcal B test strains M14459 (fHBP), 96217 (NadA), NZ98/254 (PorA) and M07-0241084 9 (NHBA). Each of these strains measures bactericidal activity primarily directed against one of the major bactericidal antigens included in the vaccine: strain M14459 measures hSBA against the fHBP variant 1.1; strain 96217 measures hSBA against antigen NadA; strain M07-0241084 measures hSBA against antigen NHBA and strain NZ98/254 measures hSBA against PorA P1.4, the immunodominant antigen in the OMV NZ vaccine component.

In case of insufficient blood volume to perform assays for all antigens, the sample will be analyzed according to priority ranking provided in Table 7.3-2.

Table 7.3-2: Immunological readouts and priority testing

Sample time points	Groups	No. of Subjects	Assay (strain/serogroup)	Priority rank
Follow-on subjects : Day 1, Day 6, Day 31 Naive subjects: Day 1, Day 31, Day 66, Day 91	All groups: B_0_2, ABCWY_0_2,ABCWY_0_6, ABCWY_0_2_6 Naive_ABCWY Naive_B	Up to 652 Follow-on subjects 200 Naive subejcts	fHBP	1
			NHBA	2
			NadA	3
			PorA	4
			Serogroup C	5
			Serogroup Y	6
			Serogroup W	7
			Serogroup A	8

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

8. STATISTICAL CONSIDERATIONS

8.1 Endpoints

8.1.1 Primary Endpoint(s)

8.1.1.1 Primary Effectiveness Endpoint(s)

This study does not have primary effectiveness endpoints.

(Amended 4 April 2018)

8.1.1.2 Primary Immunogenicity Endpoint(s)

The following will be summarized at 24 months after the last meningococcal vaccination for all follow-on subjects and at Day 1 in the extension study for naïve subjects:

- ***Percentages of subjects with HT-hSBA titers ≥LLOQ against each of four serogroup B test strains,[1] and against N. meningitidis serogroups A, C, W and Y (only for MenABCWY groups).***
- ***HT-hSBA GMTs against each of four serogroup B test strains,[1] and against N. meningitidis serogroups A, C, W and Y (only for MenABCWY groups).***

(Amended 4 April 2018)

8.1.1.3 Primary Safety Endpoint(s)

This study does not have primary safety endpoints.

(Amended 4 April 2018)

8.1.2 Secondary Endpoint(s)

8.1.2.1 Secondary Effectiveness Endpoint(s)

This study does not have secondary effectiveness endpoints.

(Amended 4 April 2018)

[1] Serogroup B test strains to be used in the study: M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA) and M07-0241084 (NHBA)

8.1.2.2 Secondary Immunogenicity Endpoint(s)

The following will be summarized at Days 1 (except four-fold rise), 6 and 31 for follow-on subjects, and at Days 1, 31, 66 and 91 for naive subjects

- Percentages of subjects with HT-hSBA titers ≥ LLOQ and differences between groups against each of four serogroup B test strains[1] and serogroups A, C, W and Y (only after MenABCWY vaccination).
- HT-hSBA GMTs and group ratios against each of four serogroup B test strains[1] and serogroups A, C, W and Y (only after MenABCWY vaccination), and GMRs (Day 6/Day1 and Day 31/Day 1 for follow-on subjects; Day 31/Day 1, Day 66/Day 1 and Day 91/Day 1 for naive subjects).
- Percentages of subjects with four-fold rise[2] in HT-hSBA titers and group differences, against each of four serogroup B test strains[1] and serogroups A, C, W and Y (only after MenABCWY vaccination).

(Amended 4 April 2018)

8.1.2.3 Secondary Safety Endpoint(s)

Safety of the study vaccines will be assessed in all subjects in terms of the percentages of subjects with reported adverse events including:

- Any solicited and unsolicited AEs reported within 30 minutes after vaccination at Day 1 (for all subjects) and also Day 61 (for naive subjects only);
- Solicited local and systemic AEs reported from Day 1 (6 hours) to Day 7 after vaccination at Day 1 (for all subjects) and Day 61 ***to Day 67*** (for naive subjects);
- Other indicators of reactogenicity (e.g. use of analgesics / antipyretics, body temperature) within 7 days after vaccination at Day 1 (for all subjects) and Day 61 (for naive subjects);
- Unsolicited AEs reported from Day 1 to Day 31 for all subjects and Day 61 to Day 91 for naive subjects;

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[1] Serogroup B test strains to be used in the study: M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA) and M07-0241084 (NHBA).

[2] For subjects with prevaccination hSBA titers < LLOQ, a post-vaccination hSBA ≥ 4 times the LLOQ; for subjects with prevaccination hSBA titers ≥ LLOQ, an increase of at least 4 times the prevaccination hSBA.

- Medically-attended AEs reported during the entire study period (up to ***D***ay 181 for follow-on subjects and up to Day 241 for naive subjects);
- AEs leading to premature withdrawal from the study during the entire study period (up to ***D***ay 181 for follow-on subjects and up to Day 241 for naive subjects);
- SAEs reported during the entire study period (up to ***D***ay 181 for follow-on subjects and up to Day 241 for naive subjects).

(Amended 4 April 2018)

8.1.3 Exploratory Endpoint(s)

8.1.3.1 Exploratory Effectiveness Endpoint(s)

This study does not have exploratory effectiveness endpoints.

(Amended 4 April 2018)

8.1.3.2 Exploratory Immunogenicity Endpoint(s)

This study does not have exploratory immunogenicity endpoints.

8.1.3.3 Exploratory Safety Endpoint(s)

This study does not have exploratory safety endpoints.

8.2 Success Criteria

8.2.1 Success Criteria for Primary Objective(s)

8.2.1.1 Success Criteria for Primary Effectiveness Objective(s)

Not applicable

(Amended 4 April 2018)

8.2.1.2 Success Criteria for Primary Immunogenicity Objective(s)

This study does not have success criteria for the primary objectives.

(Amended 4 April 2018)

8.2.1.3 Success Criteria for Primary Safety Objective(s)

Not applicable.

8.2.2 Success Criteria for Secondary Objective(s)

This study does not have success criteria for secondary objectives.

8.2.2.1 Success Criteria for Secondary Effectiveness Objective(s)

Not applicable.

(Amended 4 April 2018)

8.2.2.2 Success Criteria for Secondary Immunogenicity Objective(s)

This study does not have success criteria for secondary immunogenicity objectives.

8.2.2.3 Success Criteria for Secondary Safety Objective(s)

This study does not have success criteria for secondary safety objectives.

8.3 Analysis Sets

8.3.1 All Enrolled Set

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

8.3.2 Exposed Set

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

8.3.3 Safety Set

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

All subjects in the Exposed Set with any solicited adverse event data and/or indicators of solicited adverse events.

Unsolicited Safety Set (unsolicited adverse events)

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

Overall Safety Set

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

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

8.3.4 Full Analysis Set (FAS) Immunogenicity Set

Full Analysis Set Immunogenicity

Full Analysis Set Persistence (24 months after last vaccination in V102_15) – FAS Persistence (Day 1)

All subjects in the All Enrolled Set, who are randomized (if naive), and:

- Provide evaluable serum sample with results for at least one serogroup B test strain or serogroups A, C, W or Y at Day 1 in the extension study.

Full Analysis Set Immunogenicity (Day 31, after booster dose [follow-on]/first dose [naive]) – FAS Immunogenicity (Day 31)

All subjects in the All Enrolled Set, who are randomized (if naive), and:

- Receive at least one study vaccination and,
- Provide evaluable serum sample with results for at least one serogroup B test strain or serogroups A, C, W or Y (only after MenABCWY vaccination) at Day 31 in the extension study.

Full Analysis Set Immunogenicity (Days 6 and 31, after booster dose [follow-on]/ Days 66 and 91 after second dose [naive]) – FAS Immunogenicity (Days 6, 31/Days 66, 91)

All subjects in the All Enrolled Set, who are randomized (if naive), and:

- Receive at least one study vaccination and,
- Provide evaluable serum sample with results for at least one serogroup B test strain or serogroups A, C, W or Y (only after MenABCWY vaccination) at Day 1, and in addition at least at Day 6 or Day 31 (follow-on subjects) / Day 66 or Day 91 (naive subjects) in the extension study.

In case of vaccination error, subjects in the FAS sets will be analyzed "as randomized" (i.e., according to the vaccine a subject was designated to receive, which may be different from the vaccine the subject actually received).

(Amended 4 April 2018)

8.3.5 Per Protocol (PP) Set Immunogenicity Set

Per Protocol (PP) Set Immunogenicity

All subjects in the FAS Immunogenicity who:

- Correctly receive all meningococcal vaccinations in the parent study (persistence objective) /all meningococcal vaccinations in the parent study and vaccinations relevant for the objective[1] in the extension study (rest of immunogenicity objectives) and,
- Have no protocol deviations leading to exclusion (see section 8.3.8 , Protocol Deviations) as defined prior to analysis and,
- Are not excluded due to other reasons defined prior to analysis (see section 8.3.8 , Protocol Deviations).

Additional requirements:

Per Protocol Set Immunogenicity (Days 6 and 31, after booster dose [follow-on]/ Days 66 and 91 after second dose [naive]) – PPS Immunogenicity (Days 6, 31/Days 66, 91)

All subjects in the PPS ***Immunogenicity*** who:

- Provide evaluable serum sample with results for at least one serogroup B test strain or serogroups A, C, W or Y (only after MenABCWY vaccination) at Day 1, Day 6 and Day 31 (follow-on subjects) / Day 1, Day 66 and Day 91 (naive subjects) in the extension study.

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

[1] Booster dose (follow-on) and first dose (naive in secondary objectives ***1*** and ***3***) / first and second dose (naive in secondary objectives ***2*** and ***4***). Further details will be provided in the Statistical Analysis Plan.

Subjects might be excluded due to other reasons than protocol deviations (e.g., subjects who withdrew informed consent).

(Amended 4 April 2018)

8.3.6 Other Analysis Sets

Not applicable.

8.3.7 Subgroups

Analysis of the primary objective will be repeated and stratified by country, gender and race using the FAS and the PPS.

8.3.8 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. A protocol deviation may be a reason to remove data from an analysis set at the time of analysis. CSR-reportable protocol deviations will be defined as exclusionary from the analysis according to protocol objectives and endpoints, which will be specified in the statistical analysis plan. In some cases exclusion of data may be due to a reason other than a protocol deviation, e.g. early termination.

8.4 Statistical Analysis Plan

8.4.1 Analysis of Demographic and Baseline Characteristics

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

Distributions of subjects by age, sex and ethnic origin will be summarized overall and by vaccine group.

8.4.2 Analysis of Primary Objective(s)

8.4.2.1 Analysis of Primary Effectiveness Objective(s)

This study does not have primary effectiveness objectives.

(Amended 4 April 2018)

8.4.2.1.1 Statistical Hypotheses

Not applicable.

(Amended 4 April 2018)

8.4.2.1.2 Analysis Sets

Not applicable.

(Amended 4 April 2018)

8.4.2.1.3 Statistical Methods

Not applicable.

(Amended 4 April 2018)

8.4.2.2 Analysis of Primary Immunogenicity Objective(s)

8.4.2.2.1 Statistical Hypotheses

This study does not have statistical hypotheses pertaining to the primary immunogenicity objective.

(Amended 4 April 2018)

8.4.2.2.2 Analysis Sets

The analysis set to be used for all primary immunogenicity objectives in the Full Analysis Set. Analysis of the objectives will, in any case, be based on both the Full Analysis Set and the Per Protocol Set.

(Amended 4 April 2018)

8.4.2.2.3 Statistical Methods

For each N. meningitidis serogroup B test strain (M14459, M07-0241084, 96217 and NZ89/254) and for each of the serogroups A, C, W nd Y the percentages of subjects with HT-hSBA titers ≥LLOQ and the corresponding exact two-sided 95% CIs based on the Clopper-Pearson method will be calculated at Day 1 (i.e. approximately 24 months after the last meningococcal vaccination in study V102_15 for follow-on subjects, and Day 1 for naïve subjects). The CIs for the rate difference will be constructed using the method of Miettinen and Nurminen (*Miettinen *and Nurminen, 1985).

The hSBA titers at visit 1 Day 1 for each study group will be logarithmically transformed (base10) to fulfil the normal distribution assumption. For each N. meningitidis serogroup B test strain (M14459, M07-0241084, 96217, and NZ98/254) and serogroups A, C, W, and Y, the GMTs will be calculated with their associated two-sided 95% CIs, by exponentiating the corresponding log-transformed means and their 95% CIs obtained from the Analysis of Variance (ANOVA) model with study center included as an independent variable. Between-group ratios of GMTs will be calculated by exponentiating the between-group difference in the least square means of the log-transformed titers and the 95% CIs. In addition, a reverse cumulative distribution plot of each measure will be created.

(Amended 4 April 2018)

8.4.2.3 Analysis of Primary Safety Objective(s)

This study does not have primary safety objectives.

8.4.2.3.1 Analysis of Extent of Exposure

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

8.4.2.3.2 Analysis of Solicited Local, Systemic and Other Adverse Events

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

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

Post-vaccination solicited adverse events reported from ***D***ay 1 to ***D***ay 7 will be summarized for the intervals ***D***ay 1-3, ***D***ay 4-7, ***D***ay 1-7 by maximal severity and by vaccine group, excluding the 30 minute***s*** measurement, which will be summarized separately. The severity of solicited local adverse events, including injection-site erythema and induration will be summarized according to categories based on linear measurement: None (0-24 mm), Mild (25-50 mm), Moderate (51-100 mm), Severe (>100 mm).

Injection site pain/tenderness and systemic adverse events (except fever) occurring up to 7 days after each vaccination will be summarized according to “mild”, “moderate” or “severe”.

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

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

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

Body temperature will be summarized by 0.5 °C and 1.0 °C increments from 36.0 °C up to ≥40 °C and will be broken down according by route of measurement.

8.4.2.3.3 Analysis of Unsolicited Adverse Events

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

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

Separate summaries will be produced for the following categories:

- Serious adverse events.
- Adverse events that are possibly or probably related to vaccine.
- Adverse event leading to withdrawal.
- Adverse events leading to a medically attended visit.

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

8.4.2.3.4 Analysis of Safety Laboratory Values

Not applicable.

8.4.3 Analysis of Secondary Objective(s)

8.4.3.1 Analysis of Secondary Effectiveness Objective(s)

This study does not have secondary effectiveness objectives.

(Amended 4 April 2018)

8.4.3.1.1 Statistical Hypotheses

Not applicable.

(Amended 4 April 2018)

8.4.3.1.2 Analysis Sets

Not applicable.

(Amended 4 April 2018)

8.4.3.1.3 Statistical Methods

Not applicable.

(Amended 4 April 2018)

8.4.3.2 Analysis of Secondary Immunogenicity Objective(s)

8.4.3.2.1 Statistical Hypotheses

This study does not have statistical hypotheses pertaining to the secondary immunogenicity objective.

8.4.3.2.2 Analysis Sets

The analysis set to be used for all secondary immunogenicity objectives is the Full Analysis Set. Analysis of the objectives will, in any case, be based on both the Full Analysis Set and the Per Protocol Set.

8.4.3.2.3 Statistical Methods

For each *N. meningitidis* serogroup B test strain (M14459, M07-0241084, 96217and NZ98/254) the percentages of subjects with HT-hSBA titers ≥ LLOQ and the corresponding exact two-sided 95% CIs based on Clopper-Pearson method (Clopper and

Pearson, 1934) will be calculated at Day 1, Day 6 and Day 31 (follow-on) / Day 1, Day 66 and Day 91 (naive). Percentages and the corresponding CIs will also be computed for subjects who are positive for at least one test strain, at least two test strains, at least three test strains, and all four test strains. The CIs for the rate difference will be constructed using the method of Miettinen and Nurminen (Miettinen and Nurminen, 1985).

In addition, a reverse cumulative distribution plot of each measure will be created.

The hSBA titers at each visit for each study group will be logarithmically transformed (base10) to fulfill the normal distribution assumption. For each *N. meningitidis* serogroup B test strain (M14459, M07-0241084, 96217and NZ98/254), ***the*** GMTsand GMRs (pre-vaccination / post-vaccination) will be calculated with their associated two-sided 95% CIs, by exponentiating the corresponding log-transformed means and their 95% CIs ***obtained from the Analysis of Variance (ANOVA) model with study center included as an independent variable. Between-group ratios of GMTs and GMRs will be calculated by exponentiating the between-group difference in the least square means of the log-transformed titers and the 95% CIs.***

Percentages of subjects with four-fold titer rise, and the corresponding exact two-sided 95% CIs based on the Clopper-Pearson method against these strains will be calculated for each study group at Day 6 and Day 31 (follow-on) / Day 66 and Day 91 (naive). The CIs for the rate difference will be constructed using the method of Miettinen and Nurminen.

(Amended 4 April 2018)

8.4.3.3 Analysis of Secondary Safety Objective(s)

8.4.3.3.1 Analysis of Extent of Exposure

Extent of exposure will be assessed in terms of the frequency and percentage of exposed subjects, summarized overall and by vaccine group.

8.4.3.3.2 Analysis of Solicited Local, Systemic and Other Adverse Events

Safety of the study vaccines will be assessed in all subjects in terms of the frequency and percentage of reported AEs. See section 8.4.2.3.2 for additional details.

8.4.3.3.3 Analysis of Unsolicited Adverse Events

Safety of the study vaccines will be assessed in all subjects in terms of the frequency and percentage of reported AEs. See section 8.4.2.3.3 for additional details.

8.4.3.3.4 Statistical Hypotheses

Not applicable.

8.4.3.3.5 Analysis Sets

Safety Set (solicited adverse events and other solicited reactions), Safety Set (unsolicited adverse events), Safety Set (overall).

8.4.3.3.6 Statistical Methods

Not applicable.

8.4.4 Analysis of Exploratory Objectives

8.4.4.1 Analysis of Exploratory Effectiveness Objective(s)

This study does not have exploratory effectiveness objectives.

(Amended 4 April 2018)

8.4.4.2 Analysis of Exploratory Immunogenicity Objective(s)

This study does not have exploratory immunogenicity objectives.

8.4.4.3 Analysis of Exploratory Safety Objective(s)

This study does not have exploratory safety objectives.

8.5 Sample Size and Power Considerations of Primary Objective

Not applicable.

(Amended 4 April 2018)

8.6 Interim Analysis

No interim analysis of data from this study is planned.

9. SOURCE DOCUMENTATION, STUDY MONITORING AND AUDITING

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

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

9.1 Source Documentation

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

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

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

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

Adverse Event eCRF (AE eCRF). The AE eCRF must also capture which source(s) of information were used to determine the adverse event (e.g., subject recall, medical chart, Subject eDiary).

The Subject eDiary source data is hosted by a vendor engaged for this study, on behalf of the study investigators. Each investigator will be provided with a certified archive copy of all diary data relating to subjects at that site and must confirm it is readable.

9.2 Study Monitoring, Auditing and Source Data Verification

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

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

Contact details for the GSK team or its designee involved in study monitoring will be provided to the investigator. Study data recorded on eCRFs will be verified by checking the eCRF entries against source documents in order to ensure data completeness and accuracy as required by study protocol except for those parameters which are specifically described in section 7. Assessments being entered directly into the EDC system.

Data verification may also be performed through a centralized review of data (e.g., checking for outliers or other anomalies). Additional documents such as the investigator site file, pharmacy records, and informed consent documentation must also be available for review if requested. Arrangements for monitoring visits will be made in advance in accordance with the monitoring plan, except in case of emergency.

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

10. DATA MANAGEMENT

10.1 Data Entry and Management

In this study, all clinical data (including, but not limited to, AE/SAEs, concomitant medications, medical history, and physical assessments), safety data, and immunogenicity data will be entered onto case report forms (eCRFs) in a timely fashion by the investigator and/or the investigator's dedicated site staff. Data entered onto eCRFs are stored on a secure website. The data collected on this secure website are assimilated into an electronic data capture (EDC) system, which is compliant with Title 21 Part 11 policies of the Code of Federal Regulations (FDA, 1997). The data system includes password protection and internal quality checks. The EDC system will be designed and validated by the Sponsor prior to activation for data entry by sites. The investigator or designated delegate must review data entered and electronically sign the eCRFs to verify their accuracy.

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

10.2 Data Clarification

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

10.3 Data Protection

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

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

11. RECORD RETENTION

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

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

12. USE OF INFORMATION AND PUBLICATION

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

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

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

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

13. ETHICAL CONSIDERATIONS

13.1 Regulatory and Ethical Compliance

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

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations: including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, GSK codes on protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki (European Council 2001/20/EC 2001; FDA,1997; ICH 1997).

13.2 Informed Consent Procedures

Eligible subjects may only be included in the study after providing written informed consent or assent, as described in section 5.1.1 , Informed Consent/Assent. Before the start of the study, the investigator will have the informed consent and any other materials that will be provided to the subjects reviewed and approved by the IRB/EC. This review and approval will be documented and stored with other study documents. The investigator or designee must fully inform the subject or legal guardian of all pertinent aspects of the study. A copy of the written informed consent will be given to the subject or the designee. The subject/designee must be allowed ample time to ask about the details of the study and to make a decision as to whether or not to participate in the study. The subject and/or legal guardian(s) **must** sign the consent form indicating their agreement to participate in the study before any study-related procedures are conducted. The informed consent process may be conducted up to 5 days prior to vaccination on ***D***ay 1. If the subject and/or legal guardian(s) is unable to read and write, a witness must be present during the informed consent discussion and at the time of informed consent signature.

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

Women of childbearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements indicated in the protocol for the duration of the study. If case of doubts on

the ability of a subject to adhere to these requirements, that subject should not be allowed in the study

Before the start of the study, the investigator will have the informed assent, the informed consent, and any other materials that will be provided to the subject and/or parent(s)/legal guardian(s) reviewed and approved by the IRB/EC. This review and approval will be documented and stored with other study documents. The investigator or designee must fully inform the subject and/or parent(s)/legal guardian(s) of all pertinent aspects of the study. A copy of the written informed consent and informed assent will be given to the subject and/or parent(s)/legal guardian(s).

In addition, the investigator or designee should explain pertinent aspects of the study in an age appropriate manner to pediatric subjects who are eligible for informed assent in accordance with local policies. The subject and parent(s)/legal guardian(s)] must be allowed ample time to ask about the details of the study and to make a decision as to whether or not to participate in the study. The subject and parent(s)/legal guardian(s)] must sign the consent/assent forms indicating their agreement to participate in the study before any study-related procedures are conducted. If the subject and/or parent(s)/legal guardian(s) are unable to read and write, a witness must be present during the informed consent/assent discussion and at the time of informed consent/assent signature.

13.3 Responsibilities of the Investigator and IRB/EC

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

The investigator also responsible for the following:

- Maintaining a list of appropriately qualified persons to whom the investigator has delegated significant study-related duties.
- Demonstrating the capability of recruiting the required number of suitable subjects within the recruitment period.

- Demonstrating sufficient time and staffing to properly conduct and complete the study within the agreed study period.
- Ensuring that all persons assisting with the study are adequately informed about the protocol, the investigational product(s), and their study-related duties and functions.
- Ensuring that appropriately trained health care professionals are responsible for all study-related medical decisions and for ensuring appropriate medical care of subjects experiencing any adverse event related to the study.
- If permission to do so is given by the subject and/or parent(s)/legal guardian(s), ensuring that the subject's primary healthcare provider is informed of the subject's participation in the study.

The investigator should not implement any deviation from, or changes of the protocol without agreement by the Sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone number(s)). In addition, the investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

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

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

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

(c) To the regulatory authority(ies).

13.4 Protocol Amendments

An amendment is a written description of change(s) to or formal clarification of a study protocol which may impact on the conduct of the clinical study, potential benefit of the clinical study, or may affect subject safety, including changes of study objectives, study design, subject population, sample sizes, study procedures, or significant administrative aspects. An administrative change of a study protocol is a minor correction or clarification that has no significant impact on the way the clinical study is to be conducted and no effect on subject safety (e.g., change of telephone number(s), logistical changes). Protocol amendments must be approved by GSK, health authorities where required, and

the IRB/EC. In cases when the amendment is required in order to protect the subject safety, the amendment can be implemented prior to IRB/EC approval. Notwithstanding, the need for formal approval of a protocol amendment, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, GSK should be notified of this action, the IRB/EC at the study site, and, if required by local regulations, the relevant health authority) should be informed within 10 working days.

14. REFERENCE LIST

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APPENDIX A AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals SA

Vaccines R &D

Clinical Study Protocol Version 4

eTrack study number and Abbreviated Title	205613 (MENABCWY-012) (V102_15E1)
Amendment number:	Amendment 2 (note: no amendment to Protocol Version 1 was issued as the protocol was not submitted externally), Final Protocol Version 4 (4 April 2018)
Amendment date:	4 APR 18
Co-ordinating author:	PPD Scientific Writer, XPE Pharma for GSK Biologicals

Rationale/background for changes:
Following up on the response (submitted on 15 September 2017) to CBER comments (received on 26 October 2016), to change the defined criterion for concluding relative vaccine effectiveness, the Company agreed to remove it from the V102_15E1 study protocol and all analyses for the vaccine effectiveness objectives to be descriptive in nature. Further to this decision, in this amendment the effectiveness of the MenABCWY vaccine using enc-hSBA will no longer be assessed in ***any*** of the V102_15E1 study objectives (primary, secondary or exploratory). ***All*** the study objectives will aim to evaluate the immunogenicity of the MenABCWY vaccine against *N. meningitidis* serogroup B test strains (M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA) and M07-0241084 (NHBA)) using HT-hSBA, accordingly.

Additionally, the following minor formatting changes were implemented for consistency and readability:

- **Table of Contents** was updated.
- **List of Tables** was updated.
- In the **List of abbreviations** removed VE, vaccine efficacy.
- Throughout the document "**d**ay" was changed to "***D***ay" for consistency (section 3.4.2, section 3.5, section 3.9, section 5.1.4, section 5.2, section 5.2.1, section 5.3, section 5.3.1, section 5.3.2, and section 5.5).
- In **section 1.1 Background** a space was added between "are" and "contained" and a full stop was added at the end of the sentence: Comprehensive reviews of MenABCWY and rMenB+OMV NZ are contained in the latest version of Investigator's Brochures (IB) supplied by GSK; these documents should be

reviewed prior to initiating the study**.**

- In **section 3.1, <u>Study visits</u>, <u>Safety phone calls</u>** an extra space was deleted after "91":

– Three safety phone calls (at Day 16, 91 -and 181 for the follow on subjects and at Day 16,76, 151 and 241 fr naïve subjects) to collect medically-attended AEs, AEs leading to study withdrawal, SAEs, and related medications and vaccinations.

- In **section 3.4.2 Tools used for data collection, Subject eDiary, bullet point 3** a space was added between "… each subject." and "For vaccination…"
- In **section 5.3.1 Follow-up clinic visit(s)**: Safety follow-up clinic visits will be performed on ***D***ay 31 after ~~the~~ each vaccination (follow on subjects at Day 31 and the naive subjects at ***D***ay 31 and ***D***ay 91).
- In **section 5.3.2 Safety follow-up calls a** space was added between "…used for the telephone call." and "The site…".
- In **section 14, Reference list**:

– The reference was list was ordered alphabetically.

– The formatting for reference was corrected to remove unnecessary paragraph marks after Human and Exp: Goldschneider, I., E. C. Gotschlich, and M. S. Artenstein. 1969. Human immunity to the meningococcus. I. The role of humoral antibodies. J. Exp.Med. 129:1307–1326.

The formatting for reference was corrected to remove unnecessary paragraph marks after Human and J: Goldschneider, I., E. C. Gotschlich, and M. S. Artenstein. 1969. Human immunity to the meningococcus. II. Development of natural immunity. J. Exp. Med. 129:1327–1348.

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

In the **Synopsis Background and Rationale and in section 1.1 Background** the following changes were made:

The best option for the control of meningococcal disease is the use of effective vaccines that would include all five of the most common serogroups responsible for invasive disease. To meet this health need, GlaxoSmithKline Vaccines is currently developing a Meningococcal ABCWY vaccine (formerly developed by Novartis Vaccines) for adolescents and adults. In the phase 2 clinical program, several formulations of the candidate vaccine (with different amounts of Outer Membrane Vesicles (OMV) and

recombinant MenB proteins) were tested and found to be well-tolerated and immunogenic. GSK performed a schedule-finding study for the MenABCWY vaccine (V102_15) in healthy adolescents aged 10 through 18 years. Subjects in this study have received either 2 doses of Men ABCWY at different schedules (0,1 months; 0,2 months; 0,6 months; 0,11 months), or 3 doses of MenABCWY (0,2,6 months), or 2 doses of the GSK Meningococcal Group B vaccine rMenB+OMV (at 0,2 months). ~~The results of this study are not yet available.~~

In the **Synopsis Background and Rationale and in section 1.2 Rationale:**

The planned extension study is primarily designed to compare the ~~effectiveness~~ ***persistence*** of 2 ***doses*** (~~given at~~ 0,2 month~~s~~ ***or 0,6 month schedules***) or 3 ***doses*** (~~given at~~ 0,2,6 month~~s~~ ***schedule***) ~~doses~~ of the GSK MenABCWY vaccine ***or 2 doses (0,2 month schedule) of GSK rMenB+OMV vaccine*** administered to healthy adolescents ~~in study V102_15, against a panel of randomly selected U.S. N. meningitides serogroup B invasive disease strains~~ at ***approximately*** 24 months after the last meningococcal vaccination in ***the parent study*** V102_15, ***compared with baseline antibody levels in vaccine naïve subjects of similar age at enrolment as measured*** ~~using the hSBA assay with endogenous complement (enc hSBA). Antibody persistence will also be evaluated using an~~ ***by*** automated Serum Bacterial Assay with exogenous human complement ***(high-throughput*** hSBA ***[***HT-hSBA***]***) ~~in comparison with antibody levels in unvaccinated naïve control subjects of similar age~~. ***The Rresponse*** to a booster dose of MenABCWY ***or rMenB+OMV*** vaccine***s*** will also be assessed in follow-on subjects who received 2 or 3 doses of MenABCWY (at 0,2-, 0,6- or 0,2,6-month schedules***), or 2 doses of rMenB+OMV, respectively,*** in the parent study, and will be compared with responses to a single dose of MenABCWY ~~in or 2 doses of~~ ***or*** MenB+OMV ~~in the parent study~~***, respectively, in vaccine*** naïve subjects. ~~The response to a booster dose of rMenB+OMV will be assessed in subjects who received 2 doses of rMenB+OMV (at 0,2 month schedule) in the parent study, and will be compared with responses to a single dose of rMenB+OMV in naïve subjects. N~~ ***Vaccine n***aïve subjects will receive 2 doses of MenABCWY or rMenB+OMV, in order to complete the schedule of treatment. All subjects will be followed for 6 months after last vaccination for safety.

In the **Synopsis Objectives and in section 2.1 Primary Objective(s), the effectiveness objectives were removed and the immunogenicity objectives were restructured as follows:**

~~**Effectiveness Objectives:**~~

~~*Primary Objective*:~~

~~*1.* To evaluate the effectiveness of 3 doses of MenABCWY (administered according to a 0, 2, 6-month schedule) against a randomly selected panel of US endemic *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal~~

~~activity at 1:4 dilution using enc-hSBA, compared with 2 doses of MenABCWY (administered according to a 0, 2-month schedule), at 24 months after the last meningococcal vaccination in study V102_15.~~

~~*Secondary Objective*:~~

~~*1.* To assess the effectiveness of 2 or 3 doses of MenABCWY (administered according to 0, 2-, and 0, 2, 6-month schedules) against a randomly selected panel of U.S. endemic *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity at 1:4 dilution using enc-hSBA, at 24 months after the last MenABCWY vaccination in study V102_15 compared with meningococcal vaccine-naive subjects at enrolment in study V102_15E1.~~

~~*Exploratory Objectives*~~

~~1. To assess the percentages of subjects without bactericidal activity at 1:4 dilution, using enc-hSBA after 2 doses of rMenB+OMV vaccine (given according to 0, 2 months schedule) or 2 doses of the MenABCWY vaccine (given according to 0, 6-month schedules), against a randomly selected panel of U.S. endemic *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity at 1:4 dilution using enc-hSBA at 24 months after last meningococcal vaccination in study V102_15 and in meningococcal vaccine-naive subjects at enrolment;~~

~~*2.* To assess the percentages of subjects without bactericidal activity at 1:4 dilution, using enc-hSBA after 2 or 3 doses of the MenABCWY vaccine (given according to 0, 2-, 0, 6- or 0, 2, 6- months schedules) or 2 doses of rMenB+OMV (at 0, 2 months), against a randomly selected panel of U.S. endemic *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity at 1:4 dilution using enc-hSBA, before first vaccination and after completion of the vaccination series in the parent study V102_15, and at 24 months after last meningococcal vaccination (Day 1 in the extension study).~~

2.1 Primary ***Immunogenicity*** Objective(s)

1. To assess the persistence of bactericidal antibodies in subjects who previously received 2 or 3 doses of MenABCWY (administered according to 0,2-, 0,6- and 0,2,6-month schedules) or 2 doses of rMenB+OMV (given at a 0,2-month schedule), 24 months after the last meningococcal vaccination in study V102_15 compared with baseline antibody levels in meningococcal naïve subjects at enrolment, as measured by percentages of subjects with HT-hSBA titers ≥LLOQ and HT-hSBA

GMTs against N. meningitidis test strains for serogroup B[1] and serogroups A, C, W, and Y.

2.2 Secondary Objective(s)

2.2.1 Secondary Immunogenicity Objectives

~~1. To assess the persistence of bactericidal antibodies in subjects who previously received 2 or 3 doses of MenABCWY (administered according to 0, 2 -, 0, 6- and 0, 2, 6-month schedules) or 2 doses of rMenB+OMV (given at a 0, 2-month schedule), at 24 months after the last meningococcal vaccination in study V102_15 compared with baseline antibody levels in meningococcal naive subjects at enrolment, as measured by percentages of subjects with HT-hSBA titers ≥ LLOQ and HT-hSBA GMTs against *N. meningitidis* test strains for serogroup B[1] and serogroups A, C, W, and Y;~~

1. ***To assess the immune response at Day 31 after a booster dose of the MenABCWY vaccine given 24 months after last meningococcal vaccination in subjects who previously received 2 or 3 doses of MenABCWY at different schedules (administered according to 0, 2-, 0, 6- and 0, 2, 6-month schedules) in study V102_15 compared with the immune response at Day 31 after a single dose of MenABCWY in naive subjects, as measured by percentages of subjects with HT-hSBA titers ≥ LLOQ, percentages of subjects with four-fold rise[2] in titers and HT-hSBA GMTs against N. meningitidis serogroups A, C, W, Y and serogroup B test strains[1];***

2. ***To assess the immune response at Day 1 (prevaccination), and at Day 6 and Day 31 after a booster dose of MenABCWY given 24 months after last meningococcal vaccination in subjects who previously received 2 or 3 doses of MenABCWY at different schedules (administered according to 0, 2-, 0, 6- and 0, 2, 6-month schedules) in study V102_15, and at Day 1 (prevaccination) and after 2 doses of MenABCWY (at Day 66 and Day 91) in naive subjects, as measured by percentages of subjects with HT-hSBA titers ≥ LLOQ, percentages of subjects with four-fold rise[2] in titers and HT-hSBA GMTs against N meningitidis serogroups A, C, W, Y and serogroup B test strains[1];***

3. ***To assess the immune response at Day 31 after a booster dose of the rMenB+OMV vaccine given 24 months after last meningococcal vaccination in***

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[1] Serogoup B test strains to be used in the study: M14459 (fHbp), 96217 (NadA0, NZ98/254 (PorA) and M07-0241084 (NHBA)

[2] For subjects with prevaccination hSBA titers < LLOQ, a post-vaccination hSBA ≥ 4 times the LLOQ; for subjects with prevaccination hSBA titers ≥ LLOQ, an increase of at least 4 times the prevaccination hSBA.

subjects who previously received 2 doses of rMenB+OMV administered according to 0, 2-month schedule in study V102_15 compared with the immune response at Day 31 after a single dose of rMenB+OMV in naive subjects, as measured by percentages of subjects with HT-hSBA titers ≥ LLOQ, percentages of subjects with four-fold rise[1] in titers and HT-hSBA GMTs against N. meningitidis serogroup B test strains[2];

4. ***To assess the immune response at Day 1 (prevaccination), and at Day 6 and Day 31 after a booster dose of the rMenB+OMV vaccine given 24 months after last meningococcal vaccination in subjects who previously received 2 doses of rMenB+OMV at 0, 2-month schedule in study V102_15, and at Day 1 (prevaccination) and after 2 doses of rMenB+OMV (at Day 66 and Day 91) in naive subjects, as measured by percentages of subjects with HT-hSBA titers ≥ LLOQ, percentages of subjects with four-fold rise[1] in titers and HT-hSBA GMTs against N. meningitidis serogroup B test strains[2].***

2.2.2 Secondary Safety Objectives

1. To evaluate safety and reactogenicity of a booster dose of MenABCWY given 24 months after last meningococcal vaccination in subjects who previously received 2 or 3 doses of MenABCWY at different schedules (administered according to 0, 2-, 0, 6- and 0, 2, 6-month schedules) in study V102_15, and after a first dose of MenABCWY in naive subjects;
2. To evaluate safety and reactogenicity of a booster dose of rMenB+OMV given 24 months after last meningococcal vaccination in subjects who previously received 2 doses of rMenB (administered according to 0, 2-month schedule) in study V102_15 and after a first dose of rMenB+OMV in naive subjects;
3. To evaluate safety and reactogenicity of 2 doses of MenABCWY or rMenB+OMV in naive subjects.

[1] For subjects with prevaccination hSBA titers < LLOQ, a post-vaccination hSBA ≥ 4 times the LLOQ; for subjects with prevaccination hSBA titers ≥ LLOQ, an increase of at least 4 times the prevaccination hSBA.
[2] Serogroup B test strains to be used in the study: M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA) and M07-0241084 (NHBA).

In the **Synopsis Study Design, Study Groups, Table 1** and in **section 3.1 Overview of study design, study groups, Table 3.1-1** the following changes were made:

V102_15 (Primary Study)		V102_15E1 ~24 months after last meningococcal vaccination in parent study	
Group	**Vaccine (schedule)**	**Group**	**Number of Subjects* (target enrolment)**
ABCWY_0_2	MenABCWY (0, 2 months)	ABCWY_0_2	up to 196 ~~(100)~~
ABCWY_0_2_6	MenABCWY (0, 2, 6 months)	ABCWY_0_2_6	up to 130 (100)
B_0_2	rMenB+OMV (0, 2 months)	B_0_2	up to 196 ~~(100)~~
ABCWY_0_6	MenABCWY (0, 6 months)	ABCWY_0_6	up to 130 ~~(100)~~
		Naive (freshly enrolled)	200 (200)

*Maximum enrolment derived from planned enrolment per group in parent trial~~; Target enrolment is based on minimum number of subjects required for enc-hSBA testing.~~

In the **Synopsis Study Design, Vaccination allocation** and in **section 3.1 Overview of study design, Vaccination allocation,** the following changes were made to clarify and for consistency throughout the document:

~~Naive subjects will be randomized 1:1 to receive MenABCWY or rMenB+OMV using IRT at visit Day 1. The vaccine allocation will occur using the randomization system at visit Day 61.~~ For naive subjects, IRT will randomly assign 1 dose of MenABCWY or rMenB+OMV, based on a 1:1 ratio. IRT will automatically schedule a second visit on Day 61 for naive subjects to receive a second dose of the same vaccine received on Day 1.

In the **Synopsis Study Procedures, Clinic visits** the following changes were made**:**

At ***D***ay 1, subjects will be assessed for eligibility and then enrolled into the study. After signing informed consent (and/or assent, as applicable), subjects will undergo a review of medical history and prior medications/vaccinations (since end of study V102_15 for follow-on subjects and since birth for naive subjects), and a physical assessment. All newly recruited subjects will be in the naive group and these will be randomized 1:1 to receive MenABCWY or rMenB+OMV using IRT. No randomization to treatment arm for follow-on subjects is required as vaccine groups remain the same as in the parent study V102_15; however, allocation of treatment will be done using IRT. A blood sample of ~20 mL will be collected at Day 1 from all subjects.

Follow-on subjects will also have a clinic visit at Day 6 for a blood draw of 20 mL. At ***D***ay 31, all subjects will have a 20 mL blood draw and a safety evaluation. Naive subjects will receive their second dose of MenABCWY or rMenB+OMV at ***D***ay 61 to complete

the series, and have 2 subsequent blood draws at ***D***ays 66 and 91. ***See Table 4 for testing schedules.***

Table 4: Sample Testing Schedule in V102_15E1

Assay Type	*Subject pool*	~~**V102_15 (parent study**~~		**V102_15 (parent study**				
		~~**Pre-vaccination**~~	~~**1 month after last meningococcal vaccination**~~	***Day 1***	***Day 6***	***Day 31***	***Day 66***	***Day 91***
~~enc-hSBA (max 120 per group)~~	~~Follow-on~~	~~√~~	~~√~~					
	~~Naïve~~		~~√~~					
HT-hSBA (all enrolled)	***Follow-on***			√	√	√		
	Naive			√		√	√	√

HT-hSBA = high throughput human serum bactericidal assay

All subjects will be followed for 6 months after last vaccination for safety and then terminated from the study in a safety phone call.

In the **Synopsis Study Procedures, Randomization** the following changes were made**:**

Randomization: an Interactive Response Technology (IRT) will be used in the study. The ***following*** ~~re are two~~ randomization process~~es~~ ***is used*** in this study:

1. Randomization into the treatment group only for the Naïve group subjects

   At Visit Day 1, prior to the study vaccination, naïve subjects will be randomized into the 2 study groups according to a 1:1 ratio, MenABCWY: rMenB+OMV.

~~2. Randomization to strains for enc-hSBA testing (to be performed in CLS, Marburg) only for Day 1 samples from extensions tudy and samples from parent study to be tested for exploratory objective #2 (see Table 4 for testing schedules).~~

   ~~A maximum of 120 subjects in each group will be tested for enc-hSBA. If more than 120 subjects are enrolled in any follow-on group, a random subset of 120 subjects will be selected for enc-hSBA testing. For Naïve subjects, a random subset of 120 subjects (out of 200 enrolled at Day 1) will be selected for enc-hSBA testing. Blood samples from subjects either from the naïve group or followon groups not selected for enc-hSBA testing will be stored at -80°C for potential future testing. See section 7.3 for details.~~

~~**Table 4: Sample Testing Schedule in V102_15E1**~~

~~Assay Type~~	~~Subject pool~~	~~V102_15 (parent study~~		~~V102_15E1 (extension study)~~				
		~~Pre-vaccination~~	~~1 month after last meningococcal vaccination~~	~~Day 1~~	~~Day 6~~	~~Day 31~~	~~Day 66~~	~~Day 91~~
~~enc-hSBA (max 120 per group)~~	~~Follow-on~~	~~√~~	~~√~~	~~√~~				
	~~Naïve~~			~~√~~				
~~HT-hSBA (all enrolled)~~	~~Follow-on~~			~~√~~	~~√~~	~~√~~		
	~~Naive~~			~~√~~		~~√~~	~~√~~	~~√~~

HT-hSBA = high throughput human serum bactericidal assay

In the **Synopsis Endpoint(s)** the following changes were made**:**

~~*Effectiveness Endpoints*~~

~~The following will be summarized for all follow-on subjects prevaccination and after last meningococcal vaccination in parent study V102_15 and at 24 months (Day 1 in extension study) after last meningococcal vaccination in study V102_15, and for naive subjects at Day 1 in the extension study.~~

~~1. The percentage of subjects without bactericidal serum activity at 1:4 dilution using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains~~

***Primary** Immunogenicity Endpoints*

The following will be summarized at 24 months after last meningococcal vaccination for all follow-on subjects and at Day 1 in extension study for naive subjects

1. Percentages of subjects with HT-hSBA titers ≥ LLOQ against each of four serogroup B test strains,[1] and serogroups A, C, W and Y ***(only for MenABCWY groups).***

2. HT-hSBA GMTs against each of four serogroup B test strains,[1] and against *N. meningitidis* serogroups A, C, W and Y ***(only for MenABCWY groups).***

[1] Serogroup B test strains to be used in the study: M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA) and M07-0241084 (NHBA).

Secondary Immunogenicity Endpoint(s)

The following will be summarized at Days 1 (except four-fold rise), 6 and 31 for follow-on subjects, and at Days 1, 31, 66 and 91 for naive subjects

1. Percentages of subjects with HT-hSBA titers ≥ LLOQ and differences between groups against each of four serogroup B test strains[1] and serogroups A, C, W and Y (only after MenABCWY vaccination).

2. HT-hSBA GMTs and group ratios against each of four serogroup B test strains[1] and serogroups A, C, W and Y (only after MenABCWY vaccination), and GMRs (Day 6/Day1 and Day 31/Day 1 for follow-on subjects; Day 31/Day 1, Day 66/Day 1 and Day 91/Day 1 for naive subjects).

3. Percentages of subjects with four-fold rise[2] in HT-hSBA titers and group differences, against each of four serogroup B test strains[1] and serogroups A, C, W and Y (only after MenABCWY vaccination).

In the **Synopsis Statistical Analyses** the following changes were made:

~~An acceptable volume of blood sample for enc-hSBA testing for each subject in this study (aged approximately 12 to 20 years) is 20 mL, from which approximately 35 (range 33-37) endemic US *N. meningitidis* serogroup B strains and four serogroup B test strains can be tested using enc-hSBA. In addition, the same sample can be used for testing 8 test strains (4 serogroup B test strains and 1 each for serogroups A, C, W and Y) using hSBA in each subject.~~

~~*Primary and secondary effectiveness objective*~~

~~Assuming 100 subjects enrolled in a group, and after accounting for a maximum of 5% subjects for whom serological results might not be available, 95 evaluable subjects are expected. The estimated number of strains to be tested per sample is approximately 35 (range 33-37), based on a 50% re-test rate. With 95 evaluable subjects in a group, this translates into approximately 30 (range 28-32) samples for assessment of vaccine efficacy (VE) for each strain and 3325 (range 3135-3515) total measures for the overall VE, for that group.~~

[1] Serogroup B test strains to be used in the study: M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA) and M07-0241084 (NHBA).

[2] For subjects with prevaccination hSBA titers < LLOQ, a post-vaccination hSBA ≥ 4 times the LLOQ; for subjects with prevaccination hSBA titers ≥ LLOQ, an increase of at least 4 times the prevaccination hSBA.

~~For each endemic US *N. meningitidis* serogroup B strain tested using the enc-hSBA, vaccine effectiveness (VE) of 3 doses of MenABCWY compared to 2 doses of MenABCWY will be defined as VE = [1 - (percentage of subjects without bactericidal serum activity at 1:4 dilution using enc-hSBA in MenABCWY group receiving 3 doses/ percentage of subjects without bactericidal serum activity at 1:4 dilution using enc-hSBA in MenABCWY group receiving 2 doses)] x 100. For the primary and secondary effectiveness endpoints for the 110 strains combined, the overall VE will be obtained by pooling across 110 individual strain-specific VE measures.~~

~~For the primary and secondary effectiveness endpoints, a log-binomial model will be estimated, with binary outcome "having/not having bactericidal serum activity at 1:4 dilution using enc-hSBA" for each strain tested within each subject. Treatment group and strain will be included as independent variables. The VE and associated 95% CI will be computed from this model. A Poisson regression with a robust error variance will be estimated as an alternative, to account for the clustering of data and in case of difficulties in convergence of the log-binomial model.~~

~~Secondary~~ Primary *i*mmunogenicity objectives~~:~~

The proportion of subjects with HT-hSBA titers ≥ LLOQ against *N. meningitidis* serogroup B test strains[1] and serogroups A, C, W and Y and associated two-sided 95% Clopper-Pearson confidence intervals (CI) will be calculated for each vaccine group ***at Day 1 (i.e. 24 months after the last meningococcal vaccination in study V102_15 for follow-on subjects, and Day 1 for naïve subjects). The CIs for the rate difference will be constructed using the method of Miettinen and Nurminen.***

HT-hSBA GMTs at Day 1 and associated two-sided 95% CIs against N meningitidis serogroups A, C, W and Y and each of four serogroup B test strains[1] will be calculated for each vaccine group using an Analysis of Variance (ANOVA) to account for imbalance of explanatory variables. Between-group ratios of GMTs will be computed and 95% confidence intervals will be calculated by exponentiating the between-group difference in the least square means (from the ANOVA) of the log-transformed titers and the 95% CIs.

[1] Serogroup B test strains to be used in the study: M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA) and M07-0241084 (NHBA).

Secondary immunogenicity objective(s)

The proportion of subjects with HT-hSBA titers ≥ LLOQ and with four-fold rise[1] in titers against N. meningitidis serogroup B test strains[2] and serogroups A, C, W and Y and associated two-sided 95% Clopper-Pearson (CI) will be calculated for each vaccine group at Day 1 (except four-fold rise), Day 6 and Day 31 (follow-on) / Day 1 Day 66, and Day 91 (naïve). The proportion will also be computed for subjects positive for at least 1, at least 2, at least 3, and all 4 test strains.

For between-group comparisons of percentages of subjects with HT-hSBA titers ≥ LLOQ, and percentages of subjects with four-fold rise[1] in titers, estimates of the difference will be provided along with the associated 95% confidence interval using the methodology of Miettinen and Nurminen.

HT-hSBA GMTs and GMRs (post-vaccination / pre-vaccination) and associated two-sided 95% CIs against N meningitidis serogroups A, C, W and Y and each of four serogroup B test strains[2] will be calculated for each vaccine group using an Analysis of Variance (ANOVA) to account for imbalance of explanatory variables. Between-group ratios of GMTs and GMRs will be computed and 95% confidence intervals will be calculated by exponentiating the between-group difference in the least square means (from the ANOVA) of the log-transformed titers and the 95% CIs.

~~The proportion of subjects with HT-hSBA titers ≥ LLOQ against N. meningitidis serogroup B test strains and serogroups A, C, W and Y and associated two-sided 95% Clopper-Pearson confidence intervals (CI) will be calculated for each vaccine group. For between-group comparisons of percentages of subjects with HT-hSBA titers ≥ LLOQ and percentages of subjects with four-fold rise in titers, estimates of the difference will be provided along with the associated 95% confidence interval using the methodology of Miettinen and Nurminen.~~

~~HT-hSBA GMTs and associated two-sided 95% CIs against N meningitidis serogroups A, C, W and Y and each of four serogroup B test strains will be calculated for each vaccine group. Between-group ratios of GMTs will be computed and 95% confidence intervals will be obtained.~~

~~For all secondary immunogenicity endpoints based on GMTs, estimates and associated 95% CIs obtained from an Analysis of Variance (ANOVA) will be provided to account~~

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[1] For subjects with prevaccination hSBA titers < LLOQ, a post-vaccination hSBA ≥ 4 times the LLOQ; for subjects with prevaccination hSBA titers ≥ LLOQ, an increase of at least 4 times the prevaccination hSBA.

[2] Serogroup B test strains to be used in the study: M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA) and M07-0241084 (NHBA).

~~for imbalance of explanatory variables.For between-group comparisons of percentages of subjects with HT-hSBA titers ≥ LLOQ and percentages of subjects with four-fold rise[1] in titers, estimates of the difference will be provided along with the associated 95% confidence interval using the methodology of Miettinen and Nurminen.~~

Secondary safety objective(s)

Further details on statistical analysis methods for safety can be found in section 8.4.3.3.

~~**Sample size and power considerations for the primary effectiveness objective**~~

~~For each strain, if the percentage of subjects without bactericidal serum activity at 1:4 dilution (enc-hSBA > 4) in the MenABCWY group receiving 2 doses is at least 60%, 30 evaluable subjects per strain and study group will provide ≥94% power to detect a vaccine effectiveness of 83%. If the percentage of subjects without bactericidal serum activity at 1:4 dilution (enc-hSBA > 4) in the MenABCWY group receiving 2 doses is at least 80%, 30 evaluable subjects per strain and study group will provide ≥97% power to detect a vaccine effectiveness of 75%.~~

~~For the overall VE, this study with 3325 measures per study group (average of 30 samples per strain and 110 strains) will provide >99% power to detect an overall VE of 33% against the panel of the endemic US *N. meningitidis* serogroup B strains with the lower limit of the two-sided 95% confidence interval >20.~~

In the **Synopsis Interim Analysis:**

None planned. Data for all primary and secondary objectves will be analyzed and reported in a final CSR after primary testing and analysis are completed. ~~Analysis of the exploratory objectives may be completed after primary analysis and the data reported in an addendum, depending on time of completion of serological testing for these objectives.~~

In **Table 5 Treatment Period-MenABCWY_0_2, MenABCWY_0_2_6, MenABCWY_0_6 and B_0_2 groups** the Visit Window (Days) cell for Clinic Visit 1 was revised to: ~24 month after last meningococcal vaccination (-1/+3 months)

In the **List of Abbreviations** the following abbreviation was removed:

~~VE, vaccine efficacy.~~

In **section 1.1 Background** a space was added between “are” and “contained” and a full stop was added at the end of the sentence: Comprehensive reviews of MenABCWY and rMenB+OMV NZ are contained in the latest version of Investigator’s Brochures (IB) supplied by GSK; these documents should be reviewed prior to initiating the study**.**

In section 3.1, Overview of study design, Vaccination allocation: ***For naive subjects, interactive response technology (IRT) will randomly assign 1 dose of MenABCWY or rMenB+OMV, based on a 1:1 ratio. IRT will automatically schedule a second visit on Day 61 for naive subjects to receive a second dose of the same vaccine received on Day 1.***

In **section 3.1, Overview of study design, Study visits, Safety phone calls** an extra space was deleted after "91":

Three safety phone calls (at Day 16, 91 -and 181 for the follow on subjects and at Day 16,76, 151 and 241 fr naïve subjects) to collect medically-attended AEs, AEs leading to study withdrawal, SAEs, and related medications and vaccinations.

In **section 3.5 Collection of clinical specimens, Blood specimens, paragraph 1** the following change was made (~~d~~ay to **D**ay):

A sample of approximately 20 mL sample of blood will be drawn from all follow on subjects at visits Day 1 before vaccination, and at visits Day 6 and ***D***ay 31 and from all naive subjects at Visit Day1 before the vaccination and at visits Day 31, Day 66 and Day 91. The blood volume will not exceed 20 mL at each time point. A volume of 20 mL is required in order to provide the necessary serum volume (approximately half of the blood draw volume) for the planned serology assays.

In **section 3.4.2 Tools used for data collection, Subject eDiary**, **paragraph 1:**

Electronic Diaries (eDiaries) (refer to the eDiary Implementation and Compliance Summary for details), hereafter referred to as Subject eDiaries will be the only source document allowed for solicited local and systemic adverse events (including body temperature measurements), starting after the initial 30 minute***s*** post-vaccination period at the clinic till ***D***ay 7 after the vaccination (or until resolution, in case of solicited AEs ongoing after ***D***ay 7).

In **section 3.4.2 Tools used for data collection, Subject eDiary, bullet point 3:**

A space was added between "… each subject." and "For vaccination…"

In section 3.5 Collection of clinical specimens, Blood specimens:

All the aliquots will be stored at a temperature of ~~-80°C or lower~~ ***-18°C or below***.

In **section 3.9 End of study, paragraph 2** the following changes was made (~~d~~ay to **D**ay):

A subject is considered to have completed the study when he/she has completed the last study visit/contact (Follow on subjects at Day 181 and the naive subjects at ***D***ay 241) and provided safety information.

In **section 3.5 Collection of clinical specimens, Urine specimens, paragraph 1** the following change was made (~~d~~ay to **D**ay):

Urine will be collected for pregnancy testing in females of child bearing potential. Urine will be collected at visit Day 1 (all) and ***D***ay 61 (naive) before vaccination, and the results recorded in the source document and eCRF.

In **section 5.1.4 Randomization, paragraphs 4 and 5** the following changes were made (**d**ay to **D**ay):

For follow on subjects, on Visit ***D***ay 1, IRT will assign a pack ID of the same treatment received in the V102_15 (MenABCWY or rMenB+OMV).

For Naive subjects, IRT will randomly assign 1 dose of MenABCWY or rMenB+OMV, based on a 1:1 ratio. IRT will automatically schedule a second visit on Day 61 for naive subjects to receive a second dose of the same vaccine received on ***D***ay 1.

In **section 5.2 Vaccination Clinic Visit(s), paragraphs 1 and 4** the following changes were made (~~d~~ay to **D**ay):

Paragraph 1: The first vaccination will be performed on ***D***ay 1 for all subjects. The naive subjects will receive their second dose at Day 61 visit.

Paragraph 2: After completing the pre-vaccination procedures on ***D***ay 1 for all subjects and at Day 61 for naive subjects, administer the vaccine to the subject according to the procedures described in section 6.3, Vaccine Preparation and Administration.

In **section 5.2.1 Post-vaccination Procedure, paragraph 1** the following change was made (~~d~~ay to **D**ay):

The following post-vaccination procedures will be performed on ***D***ay 1 for all subjects and at ***D***ay 61 for the naive.

In **section 5.3 Post-vaccination visits** the following minor edits were made:

A space preceding “Follow” was removed: -Follow on subjects: 5 days after the vaccination to collect the blood sample, 30 days after the vaccination to evaluate the subject’s safety and to collect the blood sample.

A space was added after “…second vaccination (Day 66)…” and **d**ay was changed to **D**ay: Naive subjects: 30 days after the first vaccination to collect a blood sample and evaluate the subject’s safety and 5 days after the second vaccination (Day 66) to collect the blood sample and 30 days (***D***ay 91) after the second vaccination to evaluate the subject’s safety and to collect the blood sample.

In **section 5.3.1 Follow-up clinic visit(s)** the following change was made**:**

Safety follow-up clinic visits will be performed on ***D***ay 31 after ~~the~~ each vaccination (follow on subjects at Day 31 and the naive subjects at ***D***ay 31 and ***D***ay 91).

In **section 5.3.2 Safety follow-up calls, paragraphs 1 and 2** the following changes were made:

Paragraph 1 - Safety follow-up calls will be performed on Day 16 after each vaccination (all subjects at ***D***ay 16 and the naive subjects at ***D***ay 76). At least 3 attempts should be made to reach the subject or subjects's parent/legal guardian.

Paragraph 2 – A space was added after "…used for the telephone call. The site…": Safety follow-up calls are calls made to the subject or subject's parent/legal guardian 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 or parent(s)/legal guardian(s) will be interviewed according to the script, and information relating to unsolicited adverse events (AEs), serious adverse events (SAEs), medically attended adverse events, 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 activity (clinic visit) with the subject or parent(s)/legal guardian(s).

In **section 5.5 Study termination visit, paragraphs 1 to 3** the following changes were made:

The planned study termination visit will occur on ***D***ay 181 for the follow on subjects and at ***D***ay 241 for the naive subjects (6 months after the last vaccination), and will be performed by telephone call. However, in case of early terminations, the termination visit may be a clinic visit or a telephone call. The date of termination is the date of the last contact (clinic visit or telephone call) in which the subject's health status was assessed or, in cases where the subject does not agree to any further safety follow-up, it is the date consent is withdrawn. This date should be recorded on the termination eCRF page. For visit procedures to be performed for a subject whose planned study participation ends prematurely, please see section 5.5.1, Early Termination Visit.

During the telephone call (at ***D***ay 181 for the follow on subjects and ***D***ay 241 for the naive subjects), the following procedures will be performed: Collect medically-attended AEs, SAEs, and concomitant medications for these events.

The site will review with the subject and/or parent(s)/legal guardian(s) the plan of when information relating to the subject's participation in the study may be available (e.g., study results, treatment assignments). It will also be discussed how information relating to

the subject's participation in the study will be shared with the subject's healthcare provider, if the subject and/or parent(s)/legal guardian(s) chooses to share this information.

In **section 7.3 Immunogenicity Assessment** the following changes were made:

The measures of immunogenicity used in this study are standard, i.e., widely used and generally recognized as reliable, accurate, and relevant (able to describe the quality and extent of the immune response). Testing will be conducted by a GSK or designated laboratory in a blinded manner towards the treatment arm and the visit.

The functional measure of immunogenicity used in this study, Serum Bactericidal Assay (SBA), is a measure of the ability of antibodies, mediated with complement, to kill meningococci, and is widely used and generally recognized as the serological correlate of protection. Human Serum Bactericidal Assay using human complement (hSBA) for *N. meningitidis* serogroups A, C, W, Y and serogroup B strains will be performed in GSK, Clinical Laboratory Sciences, Marburg (Germany) or in a qualified and certified laboratory designated by GSK using the identical standardized, validated procedures with adequate controls. ~~Two serum bactericidal assays will be employed in this study: the endogenous complement serum bactericidal assay (enc-hSBA) for a randomly slected panel of 110 endemic US *N. meningitidis* serogroup B invasive disease strains and the High Throughput Serum Bactericidal Assay using human complement (HT-hSBA) for *N. meningitidis* serogroups A, C, W, Y and serogroup B test strains (the hSBA format used for the V102_15 parent study) will be used in this study.~~

~~Table 7.3-1. Sample Testing Schedule in V102_15E1~~

~~Assay Type~~	~~Subject pool~~	~~V102_15 (parent study)~~		~~V102_15E1 (extension study)~~				
		~~Pre-vaccination~~	~~1 month after last meningococcal vaccination~~	~~Day 1~~	~~Day 6~~	~~Day 31~~	~~Day 66~~	~~Day 91~~
~~enc-hSBA (max 120 per group)~~	~~Follow-on~~	~~√~~	~~√~~	~~√~~				
	~~Naïve~~			~~√~~				
~~HT-hSBA (all enrolled)~~	~~Follow-on~~			~~√~~	~~√~~	~~√~~		
	~~Naive~~			~~√~~		~~√~~	~~√~~	~~√~~

~~enc-hSBA Testing~~

~~Randomization to strains for enc-hSBA testing (to be performed in CLS) will be done only for Day 1 samples from extension study and samples from parent study to be tested for exploratory objective #2~~

- ~~After Visit 1, each subject from the parent study will be randomly assigned by IRT to a start strain from a randomized list of 110 US serogroup B invasive isolates. For each subject, a list of strains to be tested will be generated based on volume of serum available and retest rate. Separate lists of strains for enc-hSBA testing at baseline in the extension study and from the parent study, prevaccination and one month post last dose of meningococcal vaccination in the parent study (1 month post dose 2 or 3 depending on parent group) will be generated. For each subject, the start strain will remain the same however the number of strains to be tested at each time point will be determined by volume available.~~

- ~~A maximum of 120 subjects in each group will be tested for enc-hSBA. If more than 120 subjects are enrolled in any follow-on group, a random subset of 120 subjects will be selected for enc-hSBA testing. For Naive subjects, a random subset of 120 subjects (out of 200) will be selected for enc-hSBA testing. Blood samples from subjects either from the naive group or follow on groups not selected for enc-hBSA testing will be stored at -80°C for potential future testing.~~

- ~~At Day 1, approximately 20 mL of blood will be collected from each subject and sent to GSK Clinical Laboratory Sciences (CLS, Marburg, Germany). CLS will prepare the aliquots for enc-hSBA testing depending on the serum volume and enter the number of available aliquots into the IRT system. A random subset of 120 subjects per group will be selected for testing (if applicable).~~

- ~~Within each study group, each subject's Visit 1 serum sample will be randomly assigned by IRT to a start strain in the pre-ordered sequence of 110 invasive disease serogroup B strains (e.g., strain 101). The total number of strains to be tested for each sample will be based on the number of available aliquots and the expected re-test rate. Each subject will be assigned a start strain once, based on the Visit 1 serum sample. Serum samples from subsequent visits of the same subject will be assigned the same start strain however the number of strains may vary depending on serum volume available. Based on the expected number of strains tested and the starting strain for each subject, a pre-determined list of strains for testing each sample will be generated by IRT and provided to the lab.~~

~~Randomization of strains for enc-hSBA testing:~~

~~110 invasive serogroup B strains from the U.S. CDC collection are included in the panel for enc-hSBA testing. These strains were randomly ordered into a testing sequence for V102_16 and qualified at CLS. This same pre-ordered testing sequence (strains 1-110) will be used to assign a start strain and define the list of strains to be tested for each sample.~~

HT-hSBA

The High Throughput human Serum Bactericidal Assay using human plasma as the source of exogenous complement (HT-hSBA) will be used to measure the induction of functional complement dependent bactericidal antibodies directed against meningococcal serogroups A, C, W and Y and serogroup B strains following the study vaccination. The key measures of immunogenicity will be the percentages of subjects with hSBA ≥ LLOQ, hSBA GMTs, and the percentage of subjects with four-fold titer rise against serogroups A, C, W and Y and serogroup B strains. A post-vaccination hSBA titer ≥4 is used as an accepted correlate of protection against invasive meningococcal disease (Goldschneider et al, 1969a; Goldschneider et al 1969b). ***The sample testing schedule is summarized in Table 7.3-1.***

Table 7.3-1: Sample Testing Schedule in V102_15E1

Assay Type	*Subject pool*	*V102_15E1 (extension study)*				
		Day 1	***Day 6***	***Day 31***	***Day 66***	***Day 91***
HT-hSBA (all enrolled)	*Follow-on*	√	√	√		
	naive	√		√	√	√

HT-hSBA = high throughput human serum bactericidal assay

Serum bactericidal activity against *N. meningitidis* serogroup B strains will be determined by performing HT hSBA against four meningococcal B test strains M14459 (fHBP), 96217 (NadA), NZ98/254 (PorA) and M07-0241084 9 (NHBA). Each of these strains measures bactericidal activity primarily directed against one of the major bactericidal antigens included in the vaccine: strain M14459 measures hSBA against the fHBP variant 1.1; strain 96217 measures hSBA against antigen NadA; strain M07-0241084 measures hSBA against antigen NHBA and strain NZ98/254 measures hSBA against PorA P1.4, the immunodominant antigen in the OMV NZ vaccine component.

In case of insufficient blood volume to perform assays for all antigens, the sample will be analyzed according to priority ranking provided in Table 7.3-2.

Table 7.3-2: Immunological readouts and priority testing

Sample time points	**Groups**	**No. of Subjects**	**Assay (strain/serogroup)**	**Priority rank**
Follow-on subjects : Day 1, Day 6, Day 31 Naive subjects: Day 1, Day 31, Day 66, Day 91	All groups: B_0_2, ABCWY_0_2,ABCWY_0_6, ABCWY_0_2_6 Naive_ABCWY Naive_B	Up to 652 Follow-on subjects 200 Naive subejcts	fHBP	1
			NHBA	2
			NadA	3
			PorA	4
			Serogroup C	5

Sample time points	Groups	No. of Subjects	Assay (strain/serogroup)	Priority rank
			Serogroup Y	6
			Serogroup W	7
			Serogroup A	8

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

Section 8.1.1 Primary Endpoint(s) was restructured and sub-sections were renumbered as follows: **section 8.1.1.1 Primary effectiveness endpoint(s)** (from section 8.1.1.2), **section 8.1.1.2 Primary immunogenicity endpoint(s)** (from section 8.1.1.3), **section 8.1.1.3 Primary safety endpoint(s)** (from section 8.1.1.1).

In **section 8.1.1.1 Primary Safety Endpoint(s)**, the section number was updated to section 8.1.1.***3*** Primary Safety Endpoint(s)

In **section 8.1.1.2 Primary Effectiveness Endpoint(s)** the section number was changed to 8.1.1.***1*** and the following changes were made:

~~The percentage of subjects without bactericidal serum activity at 1:4 dilution using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at 24 months after the last meningococcal vaccination in V102_15 (Day 1 in the extension study).~~ ***This study does not have primary effectiveness endpoints.***

In **section 8.1.1.3 Primary Immunogenicity Endpoint(s)**, the section number was updated to section 8.1.1.***2*** Primary Immunogenicity Endpoint(s) and the following changes were made:

~~This study does not have primary immunogenicity endpoints.~~ ***The following will be summarized at 24 months after last meningococcal vaccination for all follow-on subjects and at Day 1 in the extension study for naive subjects:***

- ***Percentages of subjects with HT-hSBA titers ≥LLOQ against each of four serogroup B test strains,[1] and serogroups A, C, W and Y (only after MenABCWY vaccination).***
- ***HT-hSBA GMTs against each of four serogroup B test strains,[1] and against N. meningitidis serogroups A, C, W and Y (only after MenABCWY vaccination).***

S**ection 8.1.2. Secondary Endpoint(s)** was restructured and sub-sections were renumbered as follows: **section 8.1.2.*1* Secondary Effectiveness Endpoint(s)** (from section 8.1.2.2), **section 8.1.2.*2* Secondary Immunogenicity Endpoint(s)** (from section 8.1.2.3), **and section 8.1.2.*3* Secondary Safety Endpoint(s)** (from section 8.1.2.4)**.**

In **section 8.1.2.1 Secondary Safety Endpoint(s)**, the section number was changed to 8.1.2.***3*** and the following change was made to bullet points 2, 5, 6, and 7:

- Solicited local and systemic AEs reported from Day 1 (6 hours) to Day 7 after vaccination at Day 1 (for all subjects) and Day 61 ***to Day 67*** (for naive subjects);
- Medically-attended AEs reported during the entire study period (up to ***D***ay 181 for follow-on subjects and up to Day 241 for naive subjects);
- AEs leading to premature withdrawal from the study during the entire study period (up to ***D***ay 181 for follow-on subjects and up to Day 241 for naive subjects);
- SAEs reported during the entire study period (up to ***D***ay 181 for follow-on subjects and up to Day 241 for naive subjects).

In **section 8.1.2.2 Secondary Effectiveness Endpoint(s)** the section number was changed to 8.1.2.***1*** and the following change following changes were made:

~~The percentage of subjects without bactericidal serum activity at 1:4 dilution using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at 24 months after the last meningococcal vaccination in V102_15 (Day 1 in the extension study) and at Day 1 in the extension study for naive subjects.~~

~~The percentages of subjects will be averaged across all strains. See statistical analysis section for additional details.~~ ***This study does not have secondary effectiveness endpoints.***

In **section 8.1.2.3 Secondary Immunogenicity Endpoint(s)** the section number was changed to 8.1.2.***2*** and the following changes were made:

[1] Serogroup B test strains to be used in the study: M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA), and M07-0241084 (NHBA).

~~The following will be summarized at 24 months after last meningococcal vaccination for all follow-on subjects and at Day 1 in extension study for naive subjects~~

- ~~Percentages of subjects with HT-hSBA titers ≥LLOQ against each of four serogroup B test strains[1] and serogroups A, C, W and Y.~~
- ~~HT-hSBA GMTs against each of four serogroup B test strains[1] and against *N. meningitidis* serogroups A, C, W and Y.~~

The following will be summarized at Days 1 (except four-fold rise), 6 and 31 for follow-on subjects, and at Days 1, 31, 66 and 91 for naive subjects

- Percentages of subjects with HT-hSBA titers ≥ LLOQ and differences between groups against each of four serogroup B test strains[1] and serogroups A, C, W and Y (only after MenABCWY vaccination).
- HT-hSBA GMTs and group ratios against each of four serogroup B test strains[1] and serogroups A, C, W and Y (only after MenABCWY vaccination), and GMRs (Day 6/Day1 and Day 31/Day 1 for follow-on subjects; Day 31/Day 1, Day 66/Day 1 and Day 91/Day 1 for naive subjects).
- Percentages of subjects with four-fold rise[2] in HT-hSBA titers and group differences, against each of four serogroup B test strains[1] and serogroups A, C, W and Y (only after MenABCWY vaccination).

Section 8.1.3 Exploratory Endpoint(s) was restructured was restructured and sub-sections were renumbered as follows: **section 8.1.3.*1* Exploratory Effectiveness Endpoint(s)** (from 8.1.3.2), **section 8.1.3.*2* Exploratory Immunogenicity Endpoint(s)** (from 8.1.3.3), and **section 8.1.3.*3* Exploratory Safety Endpoint(s)** (from 8.1.3.1)

In **section 8.1.3.1 Secondary Safety Endpoint(s)** the section number was changed to 8.1.3.***3***

In **section 8.1.3.2 Exploratory Effectiveness Endpoint(s)** the section number was changed to 8.1.3.***1*** and the following changes were made:

- ~~The percentages of subjects without bactericidal serum activity at 1:4 dilution using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at 24 months after the last vaccination in V102_15 (Day 1 in the extension study), and at Day 1 for naive subjects.~~

[1] Serogroup B test strains to be used in this study: M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA), and M07-0241084 (NHBA)

[2] For subjects with prevaccination hSBA titers < LLOQ, a post-vaccination hSBA ≥4 times the LLOQ; for subjects with prevaccination hSBA titers ≥ LLOQ, an increase of at least 4 times the prevaccination hSBA

- ~~The percentages of subjects without bactericidal serum activity at 1:4 dilution using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, before first vaccination and after completion of the vaccination series in the parent study V102_15, and at 24 months after last meningococcal vaccination in the parent study V102_15 (Day 1 in the extension study).~~

This study does not have exploratory effectiveness endpoints.

In **section 8.1.3.3 Exploratory Immunogenicity Endpoint(s)** the section number was changed to 8.1.3.***2***

Section 8.2.1 Success Criteria for Primary Objective(s) was restructured and sub-sections were renumbered as follows: **section 8.2.1.*1* Success Criteria for Primary Effectiveness Objective(s)** (from 8.2.1.2), **section 8.2.1.*2* Success Criteria for Primary Immunogenicity Objective(s)** (from 8.2.1.3), and **section 8.2.1.*3* Success Criteria for Primary Safety Objective(s)**.

In **section 8.2.1.1 Success Criteria for Primary Safety Objective(s)** the section number was changed to 8.2.1.***3***.

In **section 8.2.1.2 Success Criteria for Primary Effectiveness Objective(s)** the section number was changed to **8.2.1.*1*** and the following changes were made:

~~This study does not have success criteria for the primary effectiveness objective. (Amended 27 March 2017).~~ ***Not applicable.***

In **section 8.2.1.3 Success Criteria for Primary Immunogenicity Objective(s)** the section number was changed to 8.2.1.***2*** and the following changes were made:

~~Not applicable.~~ ***This study does not have success criteria for the primary immunogenicity objective.***

Section 8.2.2 Success Criteria for Secondary Objective(s) was restructured and sub-sections were renumbered as follows: **section 8.2.2.*1* Success Criteria for Secondary Effectiveness Objective(s)** (from 8.2.2.2), **section 8.2.2.*2* Success Criteria for Secondary Immunogenicity Objective(s)** (from 8.2.2.3), and **section 8.2.2.*3* Success Criteria for Secondary Safety Objective(s)** (from 8.2.2.1).

In **section 8.2.2.1 Success Criteria for Secondary Safety Objective(s)** the section number was changed to 8.2.2.***3***.

In **section 8.2.2.2 Success Criteria for Secondary Effectiveness Objective(s)** the section number was changed to 8.2.2.***1*** and the following changes were made:

~~This study does not have success criteria for secondary effectiveness objectives.~~ ***Not applicable.***

In **section 8.2.2.3 Success Criteria for Secondary Immunogenicity Objective(s)** the section number was changed to 8.2.2.***2***.

In **section 8.3.4 the section heading was changed as follows: Full Analysis Set (FAS) ~~Effectiveness/~~Immunogenicity Set** and the following changes were made:

~~***Full Analysis Set Effectiveness***~~

~~*Full Analysis Set Effectiveness (24 months after last vaccination in V102_15) – FAS Effectiveness (Day 1)*~~

~~All subjects in the All Enrolled Set, who are randomized (if naive), and:~~

- ~~Provide evaluable serum sample with the enc-hSBA results for at least one endemic N. meningitidis serogroup B invasive disease strain at Day 1 in the extension study.~~

~~*Full Analysis Set Effectiveness Over Time (Before and after last vaccination in V102_15) - FAS Effectiveness (Over Time)*~~

~~All subjects in the All Enrolled Set who:~~

- ~~Provide evaluable serum sample with the enc-hSBA results for at least one endemic N. meningitidis serogroup B invasive disease strain before first vaccination, after completion of the vaccination series in V102_15 and at Day 1 in the extension study.~~

Full Analysis Set Immunogenicity

Full Analysis Set Persistence (24 months after last vaccination in V102_15) – FAS Persistence (Day 1)

All subjects in the All Enrolled Set, who are randomized (if naive), and:

- Provide evaluable serum sample with results for at least one serogroup B test strain or serogroups A, C, W or Y at Day 1 in the extension study.

Full Analysis Set Immunogenicity (Day 31, after booster dose [follow-on]/first dose [naive]) – FAS Immunogenicity (Day 31)

All subjects in the All Enrolled Set, who are randomized (if naive), and:

- Receive at least one study vaccination and,
- Provide evaluable serum sample with results for at least one serogroup B test strain or serogroups A, C, W or Y (only after MenABCWY vaccination) at Day 31 in the extension study.

Full Analysis Set Immunogenicity (Days 6 and 31, after booster dose [follow-on]/ Days 66 and 91 after second dose [naive]) – FAS Immunogenicity (Days 6, 31/Days 66, 91)

All subjects in the All Enrolled Set, who are randomized (if naive), and:

- Receive at least one study vaccination and,
- Provide evaluable serum sample with results for at least one serogroup B test strain or serogroups A, C, W or Y (only after MenABCWY vaccination) at Day 1, and in addition at least at Day 6 or Day 31 (follow-on subjects) / Day 66 or Day 91 (naive subjects) in the extension study.

In case of vaccination error, subjects in the FAS sets will be analyzed "as randomized" (i.e., according to the vaccine a subject was designated to receive, which may be different from the vaccine the subject actually received).

In **section 8.3.5** the section heading was changed as follows: **Per Protocol (PP) Set ~~Effectiveness/~~Immunogenicity Set** and the following changes were made:

~~**Per Protocol (PP) Set Effectiveness**~~

~~All subjects in the FAS Effectiveness who:~~

- ~~Correctly receive all meningococcal vaccinations in the parent study and,~~
- ~~Have no protocol deviations leading to exclusion (see section 8.3.8, Protocol Deviations) as defined prior to analysis and,~~
- ~~Are not excluded due to other reasons defined prior to analysis (see section 8.3.8, Protocol Deviations).~~

Per Protocol (PP) Set Immunogenicity

All subjects in the FAS Immunogenicity who:

- Correctly receive all meningococcal vaccinations in the parent study (persistence objective) /all meningococcal vaccinations in the parent study and vaccinations

relevant for the objective[1] in the extension study (rest of immunogenicity objectives) and,

- Have no protocol deviations leading to exclusion (see section 8.3.8, Protocol Deviations) as defined prior to analysis and,
- Are not excluded due to other reasons defined prior to analysis (see section 8.3.8, Protocol Deviations).

Additional requirements:

Per Protocol Set Immunogenicity (Days 6 and 31, after booster dose [follow-on]/ Days 66 and 91 after second dose [naive]) – PPS Immunogenicity (Days 6, 31/Days 66, 91)

All subjects in the PPS Immunogenicity~~/Effectiveness~~ who:

- Provide evaluable serum sample with results for at least one serogroup B test strain or serogroups A, C, W or Y (only after MenABCWY vaccination) at Day 1, Day 6 and Day 31 (follow-on subjects) / Day 1, Day 66 and Day 91 (naive subjects) in the extension study.

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

Subjects might be excluded due to other reasons than protocol deviations (e.g., subjects who withdrew informed consent).

Section 8.4.2 Analysis of Primary Objective(s) was restructured and sub-sections were renumbered as follows: section 8.4.2.*1* Analysis of Primary Effectiveness Objective(s) (from 8.4.2.2), **section 8.4.2.*2* Analysis of Primary Immunogenicity Objective(s)** (from 8.2.4.3), **section 8.4.2.*3* Analysis of Primary Safety Objective (s)** (from 8.2.4.1) and updated for sub-sections of these.

In **section 8.4.2.1 Analysis of Primary Safety Objective(s)** the heading was renumbered to 8.4.2.***3***. The numbering for the following sections was also updated accordingly: section 8.4.2.1.1 Analysis of Extent of Exposure to 8.4.2.***3***.1, section 8.4.2.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events to 8.4.2.***3***.2, section 8.4.2.1.3 Analysis of Unsolicited Adverse Events to 8.4.2.***3***.3, section 8.4.2.1.4 Analysis of Safety Laboratory Values to 8.4.2.***3***.4.

[1] Booster dose (follow-on) and first dose (naive in secondary objectives ***1*** ~~2~~ and ***3*** 4) / first and second dose (naive in secondary objectives ***2~~3~~*** and ***4~~5~~***). Further details will be provided in the Statistical Analysis Plan.

In **section 8.4.2.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events,** the heading number was updated to 8.4.2.***3***.2 and in **paragraph 3** the following changes were made:

Post-vaccination solicited adverse events reported from ***D***ay 1 to ***D***ay 7 will be summarized for the intervals ***D***ay 1-3, ***D***ay 4-7, ***D***ay 1-7 by maximal severity and by vaccine group, excluding the 30 minute***s*** measurement, which will be summarized separately. The severity of solicited local adverse events, including injection-site erythema and induration will be summarized according to categories based on linear measurement: None (0-24 mm), Mild (25-50 mm), Moderate (51-100 mm), Severe (>100 mm).

In **section 8.4.2.2 Analysis of Primary Effectiveness Objective(s)** the heading was renumbered to 8.4.2.***1***. The numbering for the following sections was also updated accordingly: section 8.4.2.2.1 Statistical Hypotheses to 8.4.2.***1***.1, section 8.4.2.2.2 Analysis Sets to 8.4.2.***1***.2, section 8.4.2.2.3 Statistical Methods to 8.4.2.***1***.3.

In **section 8.4.2.2 Analysis of Primary Effectiveness Objective(s)** the section numbering was changed to 8.4.2.***1*** and the following text was added:

This study does not have primary effectiveness objectives.

In **section 8.4.2.2.1 Statistical Hypotheses** the section numbering was updated to 8.4.2.***1***.1 following text was added:

Not applicable.

In **section 8.4.2.2.2 Analysis Sets** the section numbering was updated to 8.4.2.***1***.2 and the following changes were made:

Not applicable. ~~The analysis set to be used is the Full Analysis Set. Analysis of the primary effectiveness objective will, in any case, be based on both the Full Analysis Set and the Per Protocol Set.~~

In **section 8.4.2.2.3 Statistical Methods** the section numbering was updated to 8.4.2.***1***.3 and the following changes were made:

Not applicable. ~~For overall and strain-specific vaccine effectiveness for the primary endpoint, the binary outcome killed/not killed at the 1:4 dilution by enc-hSBA (i.e. 1 if titer < 4 or 0 if titer ≥4) will be analyzed. The response to each strain will be treated as an independent measure with a unique underlying rate. Vaccine effectiveness is expected to vary among the strains. The overall VE will be estimated as the average of strain-specific VEs across the 110 strains chosen for this study.~~

~~VE is calculated as VE=1-RR, where RR is the relative risk of not having bactericidal serum activity at 1:4 dilution using enc-hSBA in the group receiving 3 doses of MenABCWY versus the group receiving 2 doses. Two methods will be considered for estimating RR: a log-binomial regression model and a Poisson regression model with a robust error variance. Treatment group and strain will be included as independent variables for overall VE and treatment group only for strain-specific VE.~~

~~Since convergence problems might arise with a log-binomial model, a Poisson regression model with a robust error variance ("modified Poisson regression", Zou 2004) is considered as an alternative. The use of a robust error variance leads to less conservative results in the Poisson regression, which otherwise overestimates the error for the estimated RR when applied to binomial data.~~

~~Missing effectiveness values are considered MCAR and therefore will not contain information that impact the result of the analysis (i.e., not informative). Imputation methods will therefore not be used.~~

In **section 8.4.2.3 Analysis of Primary Immunogenicity Objective(s)** the heading was renumbered to 8.4.2.***2***. The numbering for the following sections was also updated accordingly: section 8.4.2.3.1 Statistical Hypotheses to 8.4.2.***2***.1, section 8.4.2.3.2 Analysis Sets to 8.4.2.***2***.2, section 8.4.2.3.3 Statistical Methods to 8.4.2.***2***.3.

In **section 8.4.2.3 Analysis of Primary Immunogenicity Objective(s)** the section numbering was updated to 8.4.2.***2*** and the following change was made:

~~This study does not have primary immunogenicity objectives.~~

In **section 8.4.2.3.1 Statistical Hypotheses** the section numbering was updated to 8.4.2.***1***.1 and the following change was made:

This study does not have statistical hypotheses pertaining to the primary immunogenicity objective.

In **section 8.4.2.3.2 Analysis Sets** the section numbering was updated to 8.4.2.***2***.2 and the following changes were made:

~~Not applicable.~~ ***The analysis set to be used for all primary immunogenicity objectives is the Full Analysis Set. Analysis of the objectives will, in any case, be based on both the Full Analysis Set and the Per Protocol Set.***

In **section 8.4.2.3.3 Statistical Method**s the section numbering was updated to 8.4.2.***2***.3 and the following changes were made:

~~Not applicable.~~ ***For each N. meningitidis serogroup B test strain (M14459, M07-0241084, 96217 and NZ89/254) and for each of the serogroups A, C, W nd Y the percentages of subjects with HT-hSBA titers ≥LLOQ and the corresponding exact two-sided 95% CIs based on the Clopper-Pearson method will be calculated at Day 1 (i.e. approximately 24 months after the last meningococcal vaccination in study V102_15 for follow-on subjects, and Day 1 for naïve subjects). The CIs for the rate difference will be constructed using the method of Miettinen and Nurminen (Miettinen and Nurminen, 1985).***

The hSBA titers at visit 1 Day 1 for each study group will be logarithmically transformed (base10) to fulfil the normal distribution assumption. For each N. meningitidis serogroup B test strain (M14459, M07-0241084, 96217, and NZ98/254) and serogroups A, C, W, and Y, the GMTs will be calculated with their associated two-sided 95% CIs, by exponentiating the corresponding log-transformed means and their 95% CIs obtained from the Analysis of Variance (ANOVA) model with study center included as an independent variable. Between-group ratios of GMTs will be calculated by exponentiating the between-group difference in the least square means of the log-transformed titers and the 95% CIs. In addition, a reverse cumulative distribution plot of each measure will be created.

The **Section 8.4.3, Analysis of secondary objective(s)** was restructured and the sub section headings renumbered as follows: **section 8.4.3.1 Analysis of secondary effectiveness objective(s), section 8.4.3.2 Analysis of secondary immunogenicity objective(s), section 8.4.3.3 Analysis of secondary safety objectives**.

Section 8.4.3.1 Analysis of Secondary Safety Objective(s)I the section numbering was updated to 8.4.3.***3***. Subsection numbering was also updated as follows: **section 8.4.3.1.1 Statistical Hypotheses** renumbered to 8.4.3.***3***.1, **section 8.4.3.1.2 Analysis Sets** renumbered to 8.4.3.***3***.2, **section 8.4.3.1.3 Statistical Methods** renumbered to 8.4.3.***3***.3.

In **section 8.4.3.2 Analysis of Secondary Effectiveness Objective(s)** the section numbering was updated to 8.4.3.***1*** and the following text was added:

This study does not have secondary effectiveness objectives.

In **section 8.4.3.2.1 Statistical Hypotheses** the section numbering was updated to 8.4.3.***1***.1 and the following changes were made:

~~This study does not have statistical hypotheses pertaining to the secondary effectiveness objective.~~***Not applicable.***

In **section 8.4.3.2.2 Analysis Sets** the section numbering was updated to 8.4.3.***1***.2 and the following changes were made:

~~The analysis set to be used is the Full Analysis Set. Analysis of the secondary effectiveness objectives will, in any case, be based on both the Full Analysis Set and the Per Protocol Set.~~***Not applicable.***

In **section 8.4.3.2.3 Statistical Methods** the section numbering was updated to 8.4.3.***1***.3 and the following changes were made:

Not applicable. ~~The same statistical method as for the primary effectiveness endpoint will be used to evaluate the VE. VE is calculated as VE=1-RR, where RR is the relative risk of not having bactericidal serum activity at 1:4 dilution using enc-hSBA in the groups receiving 2 or 3 doses of MenABCWY versus naive subjects.~~

~~The distribution of subjects by percentages of serogroup B invasive strains killed at 1:4 dilution using enc-hSBA in each subject and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method (Clopper and Pearson, 1934) will be calculated for each study group at Day 1. For additional details, see Section 8.4.2.2.3.~~

Section 8.4.3.3 Analysis of Secondary Immunogenicity Objective(s) the section numbering was updated to 8.4.3.***2***. Subsection numbering was also updated as follows: **section 8.4.3.31 Statistical Hypotheses** to 8.4.3.***2***.1, **section 8.4.3.3.2 Analysis Sets** to 8.4.3.***2***.2, **section 8.4.3.3.3 Statistical Methods** to 8.4.3.***2***.3.

In **section 8.4.3.3.3 Statistical Methods** the section numbering was updated to 8.4.3.***2***.3 and the following changes were made:

For each *N. meningitidis* serogroup B test strain (M14459, M07-0241084, 96217and NZ98/254) the percentages of subjects with HT-hSBA titers ≥ LLOQ and the corresponding exact two-sided 95% CIs based on Clopper-Pearson method will be calculated at Day 1, Day 6 and Day 31 (follow-on) / Day 1, Day 66 and Day 91 (naive). Percentages and the corresponding CIs will also be computed for subjects who are positive for at least one test strain, at least two test strains, at least three test strains, and all four test strains. The CIs for the rate difference will be constructed using the method of Miettinen and Nurminen (Miettinen and Nurminen, 1985).

In addition, a reverse cumulative distribution plot of each measure will be created.

The hSBA titers at each visit for each study group will be logarithmically transformed (base10) to fulfill the normal distribution assumption. For each *N. meningitidis* serogroup B test strain (M14459, M07-0241084, 96217and NZ98/254), ***the*** GMTs and GMRs (post vaccination / pre-vaccination) will be calculated with their associated two-sided 95% CIs, by exponentiating the corresponding log-transformed means and their 95% CIs ***obtained from the Analysis of Variance (ANOVA) model with study center included as an independent variable. Between-group ratios of GMT and GMRs will be calculated by***

exponentiating the between-group difference in the least square means of the log-transformed titers and the 95% CIs.

Percentages of subjects with four-fold titer rise, ~~the percentages of subjects with hSBA titers ≥ LLOQ~~ and the corresponding exact two-sided 95% CIs based on the Clopper-Pearson method against these strains will be calculated for each study group at ~~Day 1,~~ Day 6 and Day 31 (follow-on) / ~~Day 1,~~ Day 66 and Day 91 (naive). ~~The ratio of GMTs and GMRs between the two study groups and the corresponding CI will be constructed by exponentiating the mean difference and the confidence limits in log10 (titer), using ANOVA with study center included as an independent variable.~~ The CIs for the rate difference will be constructed using the method of Miettinen and Nurminen.

~~For each *N. meningitidis* serogroup A, C, W and Y, the GMTs and GMRs (post vaccination / pre-vaccination) will be calculated, with their associated two-sided 95% CIs, by exponentiating the corresponding log-transformed means and their 95% CIs. The percentages of subjects with hSBA titers against *N. meningitidis* serogroups A, C, W and Y and the corresponding exact two-sided 95% CIs based on Clopper-Pearson method for each treatment group will be summarized. Two-sided 95% Clopper-Pearson CIs for the percentages will be computed at Day 1, Day 6 and Day 31 (follow-on) / Day 1, Day 66 and Day 91 (naive). The ratio of GMTs and GMRs between the two study groups and the corresponding CI will be constructed by exponentiating the mean difference and the confidence limits in log10 (titer), using ANOVA with study center included as an independent variable. The CIs for the rate difference will be constructed using the method of Miettinen and Nurminen. In addition, a reverse cumulative distribution plot of each measure will be created.~~

The **Section 8.4.4, Analysis of exploratory objective(s)** was restructured and the sub section headings renumbered as follows: **section 8.4.4.1 Analysis of exploratory effectiveness objectives, Section 8.4.4.2 Analysis of Exploratory Immunogenicity Objectives, section 8.4.4.3 Analysis of exploratory safety objectives.**

Section 8.4.4.1 Analysis of Exploratory Safety Objective(s) was renumbered to 8.4.4.***3***.

Section 8.4.4.2 Analysis of Exploratory Effectiveness Objective(s) was renumbered to 8.4.4.***1*** and the following changes were made:

This study does not have exploratory effectiveness objectives. ~~The second exploratory objective concerns the immune response in the parent study and Day 1 in the extension study for follow-on subjects, which will affect the set of subjects evaluable for the analysis in this objective, while the first objective only concerns study Day 1 for both follow-on and naive subjects.~~

~~The analysis set to be used is the Full Analysis Set. Analysis of the exploratory effectiveness objectives will, in any case, be based on both the Full Analysis Set and the Per Protocol Set.~~

~~The distribution of subjects by percentages of serogroup B invasive strains killed at 1:4 dilution using enc-hSBA in each subject and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method (Clopper and Pearson, 1934) will be calculated for each study group at Day 1. In addition, this will be calculated before first vaccination and after completion of the vaccination series in parent study V102_15, for follow-on subjects.~~

Section 8.4.4.3 Analysis of Exploratory Immunogenicity Objective(s) was renumbered to 8.4.4.***2***.

In **section 8.5 Sample Size and Power Considerations of Primary Objective** the ollowing changes were made:

Not applicable. ~~An acceptable volume of blood sample for enc-hSBA testing for each subject in this study (aged approximately 12 to 20 years) is 20 mL, from which approximately 35 (range 33-37) endemic US *N. meningitidis* serogroup B strains and four serogroup B test strains can be tested using enc-hSBA. In addition, the same sample can be used for testing 8 test strains (4 serogroup B test strains and 1 each for serogroups A, C, W and Y) using hSBA in each subject. 110 invasive serogroup B strains from the U.S. CDC collection are included in the panel for enc-hSBA testing.~~

~~Assuming 100 subjects enrolled per group, and after accounting for a maximum of 5% subjects for whom serological results might not be available, 95 evaluable subjects per group are expected. The estimated number of strains to be tested per sample is approximately 35 (range 33-37), based on a 50% re-test rate. With 95 evaluable subjects in a group, this translates into approximately 30 (range 28-32) samples for assessment of VE for each strain and 3325 (range 3135-3515) total measures for the overall VE, for that group.~~

~~Assuming 56 subjects enrolled per group, and after accounting for a maximum of 5% subjects for whom serological results might not be available, 50 evaluable subjects per group are expected. The estimated number of strains to be tested per sample is approximately 35 (range 33-37), based on a 50% re-test rate. With evaluable subjects in a group, this translates into approximately 16 (15-17) samples for assessment of VE for each strain and 1750 (range 1650-1850) total measures for the overall VE, for that group.~~

~~For each endemic US *N. meningitidis* serogroup B strain tested using the enc-hSBA, vaccine effectiveness (VE) of 3 doses of MenABCWY compared to 2 doses of MenABCWY will be defined as VE = [1 - (percentage of subjects without bactericidal serum activity at 1:4 dilution using enc-hSBA in MenABCWY group receiving 3 doses /~~

~~percentage of subjects without bactericidal serum activity at 1:4 dilution using enc-hSBA in MenABCWY group receiving 2 doses)] x 100. For the primary and secondary effectiveness endpoints for the 110 strains combined, the overall VE will be obtained by pooling across 110 individual strain-specific VE measures.~~

~~***For the primary and secondary effectiveness endpoints, a*** log-binomial model will be estimated, with binary outcome "having/not having bactericidal serum activity at 1:4 dilution using enc-hSBA" for each strain tested within each subject. Treatment group and strain will be included as independent variables. The VE and associated 95% CI will be computed from this model. A Poisson regression with a robust error variance will be estimated as an alternative, to account for the clustering of data and in case of difficulties in convergence of the log-binomial model.~~

~~Table 8.5-1 displays the power for a constant VE. Since this study evaluates persistence at approximately 2 years after the last meningococcal vaccination in the parent study, no relevant differences between low- and high-respondent strains are expected to be found at this point in time. As a consequence, no computations with varying VE assumptions are made.~~

~~Table 8.5-1: Power for overall VE against all 110 strains combined (95 subjects per group, 50% re-test rate)~~

~~% subjects without bactericidal serum activity at 1:4 dilution~~		**~~VE~~**	**~~Power~~***
~~2 doses MenABCWY (0,2-month schedule)~~	~~3 doses MenABCWY (0,2,6-month schedule)~~		
~~60%~~	~~50%~~	~~17%~~	~~0%~~
~~60%~~	~~40%~~	~~33%~~	~~>99%~~
~~60%~~	~~30%~~	~~50%~~	~~>99%~~
~~60%~~	~~20%~~	~~67%~~	~~>99%~~
~~60%~~	~~10%~~	~~83%~~	~~>99%~~

~~***L****ower bound of the two-sided 95% confidence interval for VE above 20%.~~
~~Approximately 35 strains tested per sample (range 33-37), based on a 50% re-test rate. With 95 evaluable subjects in a group, this translates into approximately 30 (range 28-32) samples for assessment of VE for each strain.~~
~~*Computed from 10,000 simulation runs, each based on SAS PROC GENMOD using the statistical method proposed in Section 1.2.~~

~~For the overall VE, this study with 3325 measures per study group (average of 30 samples per strain and 110 strains) will provide >99% power to detect an overall VE of 33% against the panel of the endemic US *N. meningitidis* serogroup B strains with the lower limit of the two-sided 95% confidence interval >20%. Even with a much smaller number of samples (e.g. 50 subjects, 1750 samples) the power of the study would not change and would be >99% to detect and overall VE of 33% with a lower limit of two-sided 95% confidence interval >20%.~~

Table 8.5-2 provides the power for different values of strain-specific VE, assuming 30 samples for assessment per strain:

Table 8.5-2: Power for strain-specific VE (95 subjects per group, 50% re-test rate)

% subjects without bactericidal serum activity at 1:4 dilution		VE	Power*
2 doses MenABCWY (0,2-month schedule)	3 doses MenABCWY (0,2,6-month schedule)		
60%	40%	33%	7.6%
60%	30%	50%	28.5%
60%	20%	67%	65.7%
60%	10%	83%	94.0%
80%	60%	25%	3.1%
80%	50%	38%	16.6%
80%	40%	50%	47.9%
80%	30%	63%	81.9%
80%	20%	75%	97.7%

*Lower bound of the two-sided 95% confidence interval for VE above 20%.
Approximately 35 strains tested per sample (range 33-37), based on a 50% re-test rate. With 95 evaluable subjects in a group, this translates into approximately 30 (range 28-32) samples for assessment of VE for each strain.
* Computed from 10,000 simulation runs, each based on SAS PROC GENMOD using the statistical method proposed in Section 1.2.

For each strain, if the percentage of subjects without bactericidal serum activity at 1:4 dilution (enc-hSBA > 4) in the MenABCWY group receiving 2 doses is at least 60%, 30 evaluable subjects per strain and study group will provide ≥94% power to detect a vaccine effectiveness of 83%. If the percentage of subjects without bactericidal serum activity at 1:4 dilution (enc-hSBA > 4) in the MenABCWY group receiving 2 doses is at least 80%, 30 evaluable subjects per strain and study group will provide ≥97% power to detect a vaccine effectiveness of 75%.

Considering a lower number of enrolled subjects (50 available subjects, 16 samples per strain), the above scenarios will provide study power of 61% and 75% respectively.

Power simulations have been done using PC SAS (SAS version 9.2).

In **Section 14, Reference list** the reference list was ordered alphabetically:

Clopper C J and Pearson ES. The use of confidential or fiducial limits illustrated in the case of the binomial. Biometrika; 26: 401-403. 1934.

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Zou G. A Modified Poisson Regression Approach to Prospective Studies with Binary Data. *Am J Epidemiol* 2004; 159(7):702-6.

~~Clopper C J and Pearson ES. The use of confidential or fiducial limits illustrated in the case of the binomial. *Biometrika*; 26: 401-403. 1934.~~

~~Miettinen O and Nurminen M.,. Comparative analysis of two rates. *Stat Med*; 4: 213-26. 1985.~~

~~Goldschneider, I., E. C. Gotschlich, and M. S. Artenstein. 1969. Human immunity to the meningococcus. I. The role of humoral antibodies. J. Exp. Med. 129:1307–1326.~~

~~Goldschneider, I., E. C. Gotschlich, and M. S. Artenstein. 1969. Human immunity to the meningococcus. II. Development of natural immunity. J. Exp. Med. 129:1327–1348~~

In **Section 14, Reference list**, the formatting for the following references was corrected to remove unnecessary paragraph marks:

- after Human and Exp:
    - Goldschneider, I., E. C. Gotschlich, and M. S. Artenstein. 1969. Human immunity to the meningococcus. I. The role of humoral antibodies. J. Exp.Med. 129:1307–1326.
- after Human and J:
    - Goldschneider, I., E. C. Gotschlich, and M. S. Artenstein. 1969. Human immunity to the meningococcus. II. Development of natural immunity. J. Exp. Med. 129:1327–1348**.**

Overview of previous clinical study protocol V102_15E1 versions:

- Clinical Study Protocol Version 1 (11 April 2016)
- Clinical Study Protocol Version 2 (22 June 2016)
- Clinical Study Protocol Version 3 (27 March 2017)

Protocol Sponsor Signatory Approval

eTrack study number and Abbreviated Title	205613 (MENABCWY-012) (V102_15E1)
IND number	NA
EudraCT number	2016-002230-69
Date of protocol	Final Protocol Version 4: 04 April 2018
Detailed Title	A Phase 2b, Open-Label, Multi-Center Study Assessing the Immunological Persistence of Antibodies at Approximately 2 years After the last Meningococcal Vaccination in Study V102_15 and the Response to a Booster dose of GSK MenABCWY or Meningococcal Serogroup B Vaccines, in Healthy Adolescents
Sponsor signatory	Daniela Toneatto Clinical and Epidemiology Project Lead
Signature	PPD
Date	13 April 2018

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