STATISTICAL ANALYSIS PLAN

Study 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**
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Phase of Development:	Phase 2b
Plan Prepared by:	PPD
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LIST OF ABBREVIATIONS

AE	Adverse Event
ANOVA	Analysis of Variance
CSR	Clinical Study Report
CRDL	Clinical Research and Development Lead
EXC	excluded from this analysis set
FAS	Full Analysis Set
IRT	Interactive Response Technology
MedDRA	Medical Dictionary for Regulatory Activities
PD	Protocol Deviation
PPS	Per Protocol Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDL	Study Delivery Lead
SP	Statistical Programmer
TFL	Tables, Figures and Listings
TOC	Table of Content

1. BACKGROUND AND RATIONALE

This SAP version 2 is based 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 (NZ98/254 (PorA), M14459 (fHbp), M07-0241084 (NHBA) and 96217 (NadA)) using HT-hSBA, accordingly.

For further details please refer to section 1.0 and appendix A of the protocol.

2. 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.

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 by percentages of subjects with HT-hSBA titers ≥ LLOQ, percentages of subjects

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

[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[3] in titers and HT-hSBA GMTs against *N meningitidis* serogroups A, C, W, Y and serogroup B test strains[4];

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[3] in titers and HT-hSBA GMTs against *N. meningitidis* serogroup B test strains[4];

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[3] in titers and HT-hSBA GMTs against *N. meningitidis* serogroup B test strains[4].

Safety Objectives

Primary Objective:

N.A

Secondary 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-

[3] 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.

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

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.

3. STUDY DESIGN

For further details please refer to section 3.0 of the protocol.

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* (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.

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**		Phone Call for Safety Assessment	Phone Call for Safety Assessment and Study Termination
Naive_ABCWY	100	20 mL	MenABCWY	Safety Phone call	20 mL	MenABCWY	20 mL	Safety Phone call	20 mL	Safety Evaluation		
Naive_B	100	20 mL	rMenB+OMV		20 mL	rMenB+OMV	20 mL		20 mL			

4. RANDOMIZATION AND BLINDING

4.1 Method of Group Assignment and Randomization

For further details please refer to section 5.1.4 of the protocol.

4.1.1 Definition of Randomization/Vaccination Errors

The list below provides some examples of potential errors that may occur during vaccination:

- Subjects got vaccinated with a vaccine different from the one assigned at randomization (PD code 120)
- Subjects got vaccinated with the correct vaccine but containing a lower volume (PD code 140.3)

A misrandomization is defined as a subject receiving a vaccine other than the one assigned by randomization. Misrandomization is a Clinical Study Report (CSR)-reportable Protocol Deviation (PD) and should be analyzed as randomized in Full Analysis Set (FAS), excluded from Per Protocol Set (PPS) and analyzed as received for Safety.

Please see section 7 of this document for a complete guidance on how vaccination errors are handled in the statistical analysis.

4.1.2 Forced Randomization

In case of supplies shortage for the next assigned vaccine according to the randomization schedule at the clinical site, the IRT system will use the forced randomization procedure in order to continue to enroll and vaccinate subjects. The system moves seamlessly to the next treatment/randomization number for which vaccine supplies are available. The site will not be aware of the forced randomization event.

The forced randomization mechanism is designed in such a dynamic way that once the inventory is fulfilled it will balance the treatment groups according to the randomization ratio. Forced randomization should be minimized by proactively preventing the supplies inventory shortage.

A forced randomization will not be considered a protocol deviation. However a sensitivity analysis should be performed to evaluate its impact, when >1% of subjects have been randomized by forced randomization.

4.2 Blinding and Unblinding

Not Applicable.

5. SAMPLE SIZE AND POWER CONSIDERATIONS

For details please refer to section 8.5 of the protocol.

Sample size/power considerations are included in the study protocol. Technical details including statistical assumptions and software are given in a separate sample size memo authored by the study Biostatistician. In the same document, a PRC statistical reviewer verified and documented the sample size/power considerations. This document was completed prior to finalization of the protocol and stored in eTMF.

6. DETERMINATION OF PROTOCOL DEVIATIONS

6.1 Definition of Protocol Deviations

CSR reportable PD are defined in accordance with ICH E3 as important PDs related to study inclusion or exclusion criteria, conduct of the trial, subject management or subject assessment resulting in the potential to jeopardize the safety or rights of the trial subjects or the scientific value of the trial.

All reportable PDs will be evaluated before the analysis and classified according to ICH into the following five categories:

- Subject developed withdrawal criteria during the study but was not withdrawn
- Underlying medical condition forbidden by the protocol or which may influence immune response (PD code 240).
- Subject had contraindication for a subsequent study vaccination but was vaccinated (PD code 220).
- Concomitant infection related to the vaccine which may influence immune response (PD code 250).

- Subject received wrong vaccine or incorrect dose
- Study vaccine was not administered at all (PD code 100)
- Vaccine administration not according to protocol (PD code 140.x).
- Randomization failure (vaccination not according to randomization) (PD code 120).

- Subject took an excluded concomitant medication
- Administration of concomitant vaccine(s) forbidden in the protocol (PD code 150.x).
- Administration of any medication forbidden by the protocol (PD code 230.x).

- Subject randomized and did not satisfy the entry criteria
- Subject did not meet entry criteria (PD code 200).
- Deviation from key study procedures
- Subject did not comply with study vaccination schedule (PD code 140.x).
- Subject did not provide any post-vaccination unsolicited safety data (PD code 115.x).

- Subject did not provide any post-vaccination solicited safety data (PD code 116.x).
- Subject did not comply with blood draw schedule (PD code 270.x).
- Serological results not available post-vaccination (PD code 110.x).
- Obvious incoherence, abnormal serology evolution or error in data (PD code 112).

CSR reportable PDs will lead to exclusion of the subject or part of the subject's data from at least one analysis set.

The number of subjects in any and by PD category will be summarized by vaccine, center and overall. Individual subject listings will be provided in an appendix, sorted by subject and by PD category.

Prior to the analysis, designated GSK staff will develop a memo that describes the PDs that led to exclusions from analysis sets. This memo will be signed off by at least the Biostatistician and the Cluster Physician and will be included in the trial master file (Exclusion Memo).

Prematurely terminating study participation for reasons such as withdrawal of consent or occurrence of adverse events (including death) is not considered as a PD. The missing assessments that should have otherwise been collected for that subject later in the study are also not considered as a PD.

6.2 Determination of Protocol Deviations

A set of listings will be provided to the Clinical Research and Development Lead (CRDL) and the Study Delivery Lead (SDL) for review according to SOP MON-11, on an ongoing basis during the study.

The listings will be programmed following the list presented in table in section 7.7, specifically using the PD codes specified in the first column.

After the review, the CRDL and the SDL will provide the Biostatistician with:

- An assessment of CSR reportable PDs based on blinded clinical data review.
- An assessment of subjects without PDs (e.g., premature withdrawals due to adverse event, withdrawal of consent) who should be excluded from an analysis set.

6.3 Exclusions of Individual Values for Safety Analysis

Some local and systemic adverse events will be directly measured by the subject and will not be subject to a reconciliation process, even if they are biologically implausible. Therefore these implausible measurements will be removed from the analysis but included in listings. Implausible measurements are summarized in the table below:

Table 6.3-1: Implausible Solicited Adverse Events

Parameter	Implausible measurements
Body temperature	≤ 33°C or ≥ 42°C
Erythema	For subjects ≥ 6 years: ≥ 900 mm Measurements < 0 mm
Induration	For subjects ≥ 6 years: ≥ 500 mm Measurements < 0 mm

7. ANALYSIS SETS

7.1 All Enrolled Set

All screened subjects who provide informed consent and provide demographic and/or other baseline screening measurements, regardless of the subject's randomization and vaccination status in the trial, and receive a subject ID.

Demography and baseline characteristics tables as well as subject listings will be produced on the All Enrolled Set.

7.2 Exposed Set

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

7.3 Full Analysis Set (FAS), Immunogenicity Set

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).

7.4 Per Protocol Set (PPS), Immunogenicity Set

Per Protocol Set Persistence (24 months after last vaccination in V102_15) – PPS Persistence (Day 1)

All subjects in the FAS Persistence 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[5] 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 Persistence 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 each visit on 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.

[5] Booster dose (follow-on) and first dose (naive in secondary objectives 2 and 4) / first and second dose (naive in secondary objectives 3 and 5).

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

7.5 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.

In case of vaccination error, subjects will be analyzed as "treated" (i.e., according to the vaccine a subject receives, rather than the vaccine to which the subject is randomized).

If a subject received the correct study vaccine (dose, batch) but from another ongoing study at the site then the subject's safety data should be included in the safety analysis.

7.5.1 Restricted Safety Set

Not applicable.

7.6 Other Analysis Set

Not applicable.

7.7 Overview of Analysis Sets by PD Code

Table 7.7-1: Safety Sets

PD code	PD Description	Study Objective/ Period	All Exposed Set	Overall Safety Set	Safety Set, Solicited AEs, Period 1, T6H-D7	Safety Set, Solicited AEs, Period 2, T6H-D7	Unsolicited Safety set
	Exclusion code		**EXPFL**	**SAFFL**	**SSS10FL**	**SSS11FL**	**SSU10FL**
100	**Study vaccine not administered AT ALL**	All Study	EXC	EXC	EXC	EXC	EXC
115	**Subject did not provide any post-vaccination unsolicited safety data**	All Study					EXC
116.1	**Subject did not provide any post-vaccination solicited safety data after vaccination 1**	All Study (follow on)/First vaccination (Naive)			EXC		
116.2	**Subject did not provide any post-vaccination solicited safety data after vaccination 2***	Second vaccination				EXC	

EXC = excluded from this analysis set.

*applicable to naive subjects only.

Table 7.7-2: Immunogenicity Sets

PD code	PD Description	Study objective/ period	FAS IMM Persistence (Day 1)	FAS IMM (Day 31)	FAS IMM (Days 6, 31/Days 66, 91)	PPS IMM Persistence (Day 1)	PPS IMM (Day 31)	PPS IMM (Days 6, 31/Days 66, 91)
	Exclusion code		**FAS10FL**	**FAS11FL**	**FAS12FL**	**PPS10FL**	**PPS11FL**	**PPS12FL**
100	**Study vaccine not administered AT ALL**	**Day 1 – End of study**		EXC	EXC		EXC	EXC
110. 100	**Serological results (A, C, W, Y and 4 B strains) are not available** **Visit not done, blood draw not done**	**Day 1**	EXC		EXC	EXC		EXC
110.d.102	**Serology results are not available** **Serological results (A, C, W, Y and 4 B strains) are not available**	**Day 1**	EXC		EXC	EXC		EXC
110. 200	**Serological results (A, C, W, Y and 4 B strains) are not available** **Visit not done, blood draw not done**	**Day 6 (follow on) Day 66 (naive)**			EXC			EXC
110.d.202	**Serology results are not available** **Serological results (A, C, W, Y and 4 B strains) are not available**	**Day 6 (follow on) Day 66 (naive)**			EXC			EXC

PD code	PD Description	Study objective/ period	FAS IMM Persistence (Day 1)	FAS IMM (Day 31)	FAS IMM (Days 6, 31/Days 66, 91)	PPS IMM Persistence (Day 1)	PPS IMM (Day 31)	PPS IMM (Days 6, 31/Days 66, 91)
110. 300	**Serological results (A, C, W, Y and 4 B strains) are not available** **Visit not done, blood draw not done**	**Day 31**		EXC	EXC (follow on only)		EXC	EXC (follow on only)
110.d.302	**Serology results are not available** **Serological results (A, C, W, Y and 4 B strains) are not available**	**Day 31**		EXC	EXC (follow on only)		EXC	EXC (follow on only)
110. 500	**Serological results (A, C, W, Y and 4 B strains) are not available** **Visit not done, blood draw not done**	**Day 91**			EXC (naive only)			EXC (naive only)
110.d.502	**Serology results are not available** **Serological results (A, C, W, Y and 4 B strains) are not available**	**Day 91**			EXC (naive only)			EXC (naive only)
112.102	**Obvious deviation from Laboratory Manual or error in laboratory data (HT-SBA)**	**Day 1**				EXC		EXC
112.202	**Obvious deviation from Laboratory Manual or error in laboratory data (HT-SBA)**	**Day 6 (follow on) Day 66 (naive)**						EXC

PD code	PD Description	Study objective/ period	FAS IMM Persistence (Day 1)	FAS IMM (Day 31)	FAS IMM (Days 6, 31/Days 66, 91)	PPS IMM Persistence (Day 1)	PPS IMM (Day 31)	PPS IMM (Days 6, 31/Days 66, 91)
112.302	**Obvious deviation from Laboratory Manual or error in laboratory data (HT-SBA)**	**Day 31**					EXC	EXC (follow on only)
112.502	**Obvious deviation from Laboratory Manual or error in laboratory data (HT-SBA)**	**Day 91**						EXC (naive only)
120.100	**Randomization failure to treatment**	**Day 1**				EXC (naive only)	EXC (naive only)	EXC (naive only)
140.100	**Vaccination not according to protocol**	**Day 1**				EXC	EXC	EXC
140.300	**Vaccination not according to protocol**	**Day 61 (Naive only)**						EXC (naive only)
150.100	**Administration of forbidden vaccine**	**Day 1 (before BS_1)**				EXC	EXC	EXC
150.300	**Administration of forbidden vaccine**	**Day 1 (after BS_1)- day 7**					EXC	EXC
150.500	**Administration of forbidden vaccine**	**-7/+7 2nd vaccination (naive only)**						EXC (naive only)
200	**Subject did not meet entry criteria**	**Day 1 – end of study**				EXC	EXC	EXC

PD code	PD Description	Study objective/ period	FAS IMM Persistence (Day 1)	FAS IMM (Day 31)	FAS IMM (Days 6, 31/Days 66, 91)	PPS IMM Persistence (Day 1)	PPS IMM (Day 31)	PPS IMM (Days 6, 31/Days 66, 91)
220	**Subject had contraindication for a subsequent study vaccination but was vaccinated**	**Day 1- Day 61 (naive only)**						EXC
230.101	**Administration of forbidden medication**	**Day 1**				EXC	EXC	EXC
230.102	**Administration of forbidden medication: ANTIBIOTICS**	**Day 1 (before BS_1)**				EXC		
230.201	**Administration of forbidden medication**	**Day 6 (follow on) Day 66 (naive)**					EXC (follow on only)	EXC
230.202	**Administration of forbidden medication: ANTIBIOTICS**	**Day 6 (follow on) Day 66 (naive)**						EXC
230.301	**Administration of forbidden medication**	**Day 31**					EXC	EXC
230.302	**Administration of forbidden medication: ANTIBIOTICS**	**Day 31 (before BS_2)**					EXC	EXC (follow on only)
230.501	**Administration of forbidden medication**	**Day 91**						EXC (naive only)
230.502	**Administration of forbidden medication: ANTIBIOTICS**	**Day 91**						EXC (naive only)
240	**Underlying medical condition forbidden by the protocol**	**Day 1- end of study**				EXC	EXC	EXC

PD code	PD Description	Study objective/ period	FAS IMM Persistence (Day 1)	FAS IMM (Day 31)	FAS IMM (Days 6, 31/Days 66, 91)	PPS IMM Persistence (Day 1)	PPS IMM (Day 31)	PPS IMM (Days 6, 31/Days 66, 91)
260.100	**Did not comply with study vaccination schedule**	**Day 1**					EXC	EXC
260.200	**Did not comply with study vaccination schedule**	**Day 61 (naive only)**						EXC
270.100	**Did not comply with blood draw schedule***	**Day 1**				EXC		EXC
270.200	**Did not comply with blood draw schedule**	**Day 6 (follow on) Day 66 (naive)**						EXC
270.300	**Did not comply with blood draw schedule***	**Day 31**					EXC	EXC (follow on only)
270.400	**Did not comply with blood draw schedule**	**Day 91**						EXC (naive only)

*e.g. BD after vaccination

FAS = Full Analysis Set; PPS=Per Protocol Set; EXC = excluded from this analysis set.

8. GENERAL ISSUES FOR STATISTICAL ANALYSES

8.1 Adjustment for Covariates

The log-transformed antibody titer at each timepoint will be analyzed using an Analysis of Variance (ANOVA) which includes the vaccine-group effect and a center effect (see section 8.3). Summary tables will show adjusted GMTs and adjusted ratios of GMTs for each vaccine group.

Binary data tables will show unadjusted percentages and "between-group" differences.

8.2 Handling of Dropouts, Missing Data

First-line analyses will be without missing values.

To minimize the effect of dropouts and missing data the study period will be divided into time intervals for statistical analysis of safety.

8.2.1 Safety Data

For unsolicited adverse events, the entire study period will be divided into the following intervals:

For solicited adverse events, the solicited study period 30 min - day 7 will be divided into: 30 min, 6h - day 3, day 4 - day 7, and 6h - day 7.

For each of the intervals the following algorithm will be applied:

1. If less than 20% of subjects are without any solicited AE data (i.e., none of the solicited adverse events has been captured) for the respective time interval, then only the Solicited Safety Set pertaining to the interval will be analyzed.
2. If 20% or more of subjects are without any solicited AE data, the missing mechanism will be analyzed by vaccine group using a newly created variable indicating whether a subject is missing the respective AE-value or not (1=AE record present; 0=AE record not present).
    a. If the percentage of missing subjects does not vary significantly between vaccine groups ($p>0.05$) then 'missing completely at random' (MCAR) is assumed and no further action is required. Data will be analyzed without the missing values.
    b. If the percentage of missing subjects varies significantly between vaccine group ($p\leq0.05$) then 'missing at random' (MAR) is assumed, i.e., the missing mechanism is conditional on the vaccine group. Imputation methods will be applied to reduce

potential bias arising from missing values (if applicable, details will be given in an addendum to the SAP, and results included in Appendix 16.1.9 of the CSR).

For solicited adverse events, imputations will be confined to analyses of any (rather than specific) solicited local adverse events and to any (rather than specific) solicited systemic adverse events.

For unsolicited adverse events, imputations will be restricted to analyses of any adverse events and serious adverse events.

8.2.2 Immunogenicity Data

Missing immunogenicity 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. The primary objectives will be analyzed using both the FAS and the PPS.

8.3 Multicenter Studies

Vaccine group effects will be investigated first using a linear model which allows for center differences, but does not consider vaccine-by-center interaction, i.e., the model only considers effects for center and vaccine. A center effect will be included in all analyses of the primary and secondary objectives.

If the statistical model does not converge due to the factor “center”, a model without center effect will be fitted instead.

The analysis of vaccine group effect split by center will be provided in Section 14 of the CSR for the primary objectives. If significant vaccine effects are found in a trial, there will be an exploration of the heterogeneity of vaccine group effects across centers. Results of vaccine by center interaction analysis will be provided in Appendix 16.1.9.

In case if center with low number of participants (e.g. N<= 5), country (Poland and Finland) will be used instead of center.

8.4 Multiple Comparisons and Multiplicity

Not applicable as there is only one primary hypothesis.

8.5 Immunogenicity/Safety/Other Subsets

Not applicable.

8.6 Subgroups

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

For details regarding the analyses by center please see section 8.3 above. Analyses by center will be presented in Section 14 of the CSR.

8.7 Data Transformation

Distributions of antibodies are generally skewed to the right (Nauta, 2010). Therefore, prior to any statistical analysis that assumes normally distributed observations, antibody titers or concentrations will be $\log_{10}$-transformed. GMTs [/GMCs] and their 95% CIs are computed by exponentiating (base 10) the least squares means and 95% CIs of the $\log_{10}$ titers.

8.8 Derived and Computed Variables

Immunogenicity

Values below the limit of quantification (recorded as "< LQ") will be set to half that limit (i.e., LQ/2).

Geometric Mean Titer/Concentration

The GMT will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}(t_i)}{n}\right\}}$$

where $t_1, t_2, \ldots, t_n$ are n observed immunogenicity titers/concentrations.

Geometric Mean Ratio

Geometric mean ratios (GMRs) measure the changes in immunogenicity titers/concentrations *within* subjects.

The GMR will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}\left(v_{ij}/v_{ik}\right)}{n}\right\}} = 10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}(v_{ij})-\log_{10}(v_{ik})}{n}\right\}}$$

where, for n subjects, v_{ij} and v_{ik} are observed immunogenicity titers/concentrations for subject i at time-points j and k, $j \neq k$.

4-fold rise

The four-fold titer rise is defined as:

- for subjects with pre-vaccination hSBA titers <LLOQ, a post-vaccination hSBA ≥4 LLOQ;
- for subjects with a pre-vaccination hSBA titers ≥LLOQ, an increase of at least four times of the pre-vaccination hSBA.

(this definition is not in alignment with the protocol 2, 22 JUN 2016, as the protocol had a mistaken in the definition of 4-fold rise. A NTF is available at the time of approval of this SAP, and an amendement of protocol may be done in future to correct it).

Duration in the Study

Duration in the study is defined in days as:

Last visit date (visit x)[a] – Enrollment date (visit 1) + 1

[a]or premature discontinuation date (in case of withdrawal from the study)

The duration is missing if one of the dates is missing or incomplete.

Solicited Adverse Events

For details see section 13.2.

Unsolicited Adverse Events

All adverse events will be characterized according to the date of occurrence related to the vaccination phase as follows:

- **Emergence before vaccination phase**: start date before the first date of injection of study vaccine.

- **Emergence during vaccination phase**: start date on or after the first date of injection of study vaccine or, adverse event increase in severity including to "serious" adverse event.

If start date is equal to the first date of injection then "timing" variable ("On injection day, before injection"/"On injection day, after injection") will be used to define whether the adverse event occur before or after the injection.

If there are several vaccinations, the adverse event will be associated with the most recent vaccination.

If an adverse event start date is missing or unknown, the adverse event will be considered as emergent.

When start and/or end dates of an adverse event are only partially known, adverse events will be categorized as emergent before, during, or after vaccination phase using the following rules:

- If the partial end date is before (<) the first study vaccination (i.e., year or year & month is/are before the first study vaccination year or year & month) then the adverse event is emergent before vaccination phase.
- If the partial start date is equal or after (≥) the first study vaccination (i.e., year or year & month is/are after or the same as the first study injection year or year & month) then the adverse event is emergent during vaccination phase.

The **maximum event severity** is the greatest severity associated with a preferred term for a reported adverse event according to the following order: Mild < Moderate < Severe. Unknown/ Missing severity is considered as severe (except for the definition of emergence).

Multiple AEs with the same PT for the same subject are counted only once (except in occurrences tables produced for posting purposes).

Vaccination-related Adverse Events are those for which the cause has been evaluated by the investigator, and recorded either as possibly related, probably related or unknown/ missing.

Safety Laboratory Data

Not applicable

Prestudy, Concomitant and Post-Vaccination Medications

A **previous medication** is a medication used only before the first study vaccination (i.e. medication end date < first study vaccination date).

A **post-vaccination medication** is a medication used only after study termination (i.e. medication start date > study termination date).

All other medications are **concomitant**.

When start and/or end dates of a medication intake are missing, the medication is considered as concomitant with the study vaccination schedule.

If the first study vaccination date is missing then the medication is considered as concomitant with the study vaccination schedule, provided that the study vaccine was administered to the subject.

For further details please refer to the technical and program specifications document stored in Home/analysis/V102/V102_15E1/purpose_1/final/prod/docs and Home/analysis/V102/V102_15E1/purpose_1/adam_1/prod/docs within the SAS Drug Development (SDD) server.

8.9 Analysis Software

All analyses will be performed using SAS Software version 9.2 or higher.

9. STUDY SUBJECTS

9.1 Disposition of Subjects and Withdrawals

All subjects who provide informed consent will be accounted for in this study. The frequencies and percentages of subjects in each analysis set, study withdrawals, subgroups, and major protocol deviations will also be presented.

The time the subjects are under observation will be summarized by vaccine and overall using summary statistics (mean, SD, minimum, median, maximum)

10. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

In general, all tables presented in CSR section 14.1 should show a Total column across vaccine groups.

10.1 Demographics

Age, height, weight, body mass index at enrolment in this extension study will be summarized by reporting the mean, standard deviation, median and range, and will be calculated by vaccine group and overall.

The frequencies and percentages of subjects by sex, country, age categories (for posting), ethnic origin, entry criteria fulfilled will be presented by vaccine group and overall. Demographic data will be tabulated for the All Enrolled, FAS persistence, PPS persistence, and Safety sets.

Demography and baseline characteristics at time of enrolment in parent study (V102_15) will also be reported (by vaccine group), in the subset of subjects from Poland and Finland, in the 4 vaccine groups of interest (ABCWY_0_2, ABCWY_0_6, ABCWY_0_2_6, B_0_2), separately for subjects subsequently enrolled and not enrolled in this current extension study (V102_15E1).

10.2 Medical History

The frequencies and percentages of subjects with medical history will be presented by MedDRA system organ class and preferred term, by vaccine group and overall. Medical history data will be tabulated for the All Enrolled.

11. IMMUNOGENICITY ANALYSIS

11.1 Blood Samples

The frequencies and percentages of subjects with blood draws will be summarized overall and by vaccine group. Data will be tabulated for the enrolled set.

11.2 Primary Objectives Analysis

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[6] and serogroups A, C, W, and Y.

11.3 Secondary Objectives Analysis

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[7] in titers and HT-hSBA GMTs against *N. meningitidis* serogroups A, C, W, Y and serogroup B test strains[6];

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

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

[7] 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 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[8] in titers and HT-hSBA GMTs against *N meningitidis* serogroups A, C, W, Y and serogroup B test strains[9];

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[8] in titers and HT-hSBA GMTs against *N. meningitidis* serogroup B test strains[9];

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[8] in titers and HT-hSBA GMTs against *N. meningitidis* serogroup B test strains[9].

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.

Statistical Methods

For each *N. meningitidis* serogroup B test strain (NZ98/254, M14459, M07-0241084 and 96217) 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

[8] 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.

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

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).

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 (NZ98/254, M14459, M07-0241084 and 96217), 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. 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. In addition, a reverse cumulative distribution plot of each measure will be created.

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.

12. EFFECTIVENESS ANALYSIS

12.1 Primary Objectives Analysis

NA

12.2 Secondary Objectives Analysis

NA

12.3 Exploratory Objectives Analysis

NA

13. SAFETY ANALYSIS

The analysis of safety assessments in this study will include summaries of the following categories of safety data collected for each subject:

- Vaccine exposure.
- Solicited local and systemic adverse events and indicators of solicited adverse events.
- Unsolicited adverse events.

13.1 Analysis of Extent of Exposure

The frequencies and percentages of subjects with vaccinations will be summarized overall and by vaccine group. Data will be tabulated for the All Enrolled Set.

13.1.1 Safety Completeness Analysis

Solicited adverse events

The safety completeness analysis on solicited adverse events aims to identify subjects who completed diary cards, irrespective of severity. The analysis will show the number of subjects with *valid data* by solicited adverse event and time point. *Valid data* in the context of the safety completeness analysis are all data entered in the diary card (including implausible values) except "Not done/unknown".

Four summaries will be produced:

1. The frequencies of subjects who provide diary cards by vaccine group.
2. For each solicited adverse event, the frequencies of subjects with *valid data* will be presented by vaccine group and timepoint: 30 min, 6h, days 2, 3, 4, 5, 6 and 7.
3. For each type of solicited adverse event (local, systemic) and indicators of solicited adverse events, such as analgesic use the frequencies of subjects *with valid data* by vaccine group, aggregated over time points: 6h - day 7.

4. For each solicited adverse event, the frequencies of subjects *with valid data* by vaccine group, aggregated over time points: 6h - day 7.

For the corresponding percentages, the denominator will be the respective numbers of exposed subjects, i.e., subjects who received a vaccination and were still in-study for that time point or time interval, irrespective of whether a ediary card was present or not.

All analyses will be based on the 'as treated' analysis set.

13.2 Solicited Local and Systemic Adverse Events

For details please refer to section 7.1.1 of the protocol.

Only solicited local and systemic adverse events reported in the diary card will be analyzed. Implausible measurements will not be taken into consideration in the analysis but listed in the Appendix (see section 6.3).

Solicited adverse events will be reported at 30 minutes, at 6 hours on day 1 and then daily until day 7 using structured diaries. The analyses of solicited adverse events will be done separately for 30 minutes and based on three intervals: 6h - day 3, day 4 - 7 and 6h - day 7, each without 30 minutes data. In addition solicited adverse events ongoing after day 7 will be presented as unsolicited AE.

For erythema and induration, recorded originally as diameters (mm), the following categorization will be used to summarize the data:

Grade 0 (< 25 mm), any (25-50 mm, 51-100 mm, >100 mm)

Body temperature will be broken down by route of measurement according to the recommendations of the Brighton collaboration and will be summarized according to the 3 schemes described below:

- by 0.5 °C increments:
- <36.0,
- 36.0 - 36.4
- 36.5 - 36.9
- 37.0 - 37.4
- 37.5 - 37.9
- 38.0 - 38.4
- 38.5 - 38.9
- 39.0 - 39.4
- 39.5 - 39.9
- ≥40.0°C

- by 1.0 °C increments:
    - <36.0,
    - 36.0 - 36.9
    - 37.0 - 37.9
    - 38.0 - 38.9
    - 39.0 - 39.9
    - ≥40.0°
- <38.0, ≥38.0 °C

Fever, defined as a body temperature of ≥38°C irrespective of route of measurement, will be integrated to the summaries as a systemic adverse event.

The analyses will encompass summaries of the data on five levels:

1. Daily reports of subjects with solicited adverse events (excluding 30 minutes on day 1).
2. Time of first onset of solicited adverse events (excluding 30 min measurement).
3. Solicited adverse events, maximum event severity by event and interval 6h - day 3, day 4 -7, and 6h - day 7, each without 30 min.
4. Duration of solicited adverse events, excluding ongoing AE after Day 7.
5. Solicited adverse events and indicators of solicited adverse events, occurrence of at least one event by category (local, systemic) and interval 6h-Day 3, Day 4-7 and 6h-Day 7, each without 30 min.

For each of the time points or time intervals presented in the summaries, only subjects with at least one plausible observation (i.e., any non-missing values but excluding "Not done/unknown" and implausible values) for the solicited adverse events in the interval of interest will be considered. Subjects without plausible data (i.e. missing values or reported as "Not done/unknown" and implausible values) will be removed from the denominator to prevent a downward bias (towards zero).

The analysis of solicited AE after first vaccination (applicable to all vaccine groups) will be reported separated from the analyses of solicited AE after second vaccination and after any vaccination (applicable only to naive subjects).

Level 1: Daily reports of solicited adverse event

For each of the time points only subjects with at least one plausible observation (i.e., any non-missing values but excluding "Not done/unknown" and implausible values) for the solicited adverse event in the interval of interest will be considered. Subjects without plausible data (i.e. missing values or reported as "Not done/unknown" and implausible values) will be removed from the denominator in order to prevent a downward bias (towards zero). Data collected will be summarized (frequencies and percentages of subjects) by vaccine group, solicited adverse event, vaccination number and time point.

Level 2: Time of first onset of solicited adverse events

The **time of first onset** is defined, for each subject, for each solicited adverse event, as the time point at which the respective solicited adverse event first occurred. For erythema, and induration the following threshold will be used ≥ 25 mm. The summary will provide the frequencies and percentages of subjects with first onset of each solicited adverse events by vaccine group and by each time point.

For each vaccination the first onset of the adverse event will be used for each subject. For any vaccination the worst adverse event across all vaccinations per time point will be used. Note, 'not done' is treated identical to 'missing'.

Level 3: Solicited adverse events, maximum event severity by event and interval

The **maximum event severity** will be defined if there is at least one plausible non-missing observation (excluding "Not done/unknown" and implausible values) within this time interval, Each subject's data will be aggregated across the time points of the interval and summarized according to the maximal severity observed for each adverse event, followed by a summary across subjects for each vaccine. Subjects without any solicited adverse events in the interval, i.e., missing values at each of the requested time points, will be removed from the denominator.

Level 4: Number of days with solicited adverse events

The number of days with the adverse event is defined irrespective of severity. This means at least 'mild' solicited adverse event that are assessed qualitatively ≥ 25, mm for erythema and induration. If a solicited adverse event continues beyond day 7 the period after day 7 is not added.

The frequency distribution of the number of days will be provided in a summary table by vaccine and by adverse event.

Level 5: Solicited adverse events, occurrence of at least one event by category (local, systemic) and interval.

The **occurrence of at least one solicited adverse event** is defined as "any" for a subject if he/she reports greater than "none" ≥ 25 mm, for erythema, and induration) for the respective event and "none" otherwise. The occurrence of at least one solicited adverse event (i.e., none versus any) will be summarized by category (i.e., local, systemic, any), by vaccine group, by vaccination (after each vaccination and after any vaccination) and by time interval.

Medications to treat or prevent pain or fever will be summarized by frequencies and percentages of subjects reporting use of the medications by interval 30 min, 6h - day 3, day 4 - 7, 6h - day 7.

13.3 Unsolicited Adverse Events

All the unsolicited adverse events occurring during the study, judged either as probably related, possibly related, or not related to vaccination by the investigator, will be recorded. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The unsolicited adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class. Adverse events judged by the investigator as at least possibly related to study vaccine will be summarized by vaccine group, according to system organ class and preferred term within system organ class. When an unsolicited adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted.

Only vaccine-emergent adverse events (see section 8.7 for definition) will be analyzed, i.e., excluding those after a subject has given informed consent but before vaccination. The selection of unsolicited adverse events and the assignment to time intervals will be done by day of onset and not by days ongoing/persisting.

The analysis of unsolicited adverse events comprises the following categories:

- Any unsolicited adverse event (from day 1 to day 31 all vaccine groups, from day 61 to day 91 and after any vaccination (day 1-31 and day 61-91) for naive groups only)
- Possibly or probably related unsolicited adverse events (from day 1 to day 31 all vaccine groups, from day 61 to day 91 and after any vaccination (day 1-31 and day 61-91) for naive groups only)
- Unsolicited adverse events leading to death (from day 1 to end of study for all vaccine groups).

- Serious adverse events (from day 1 to end of study for all vaccine groups).
- Possibly or probably related serious adverse event (from day 1 to end of study for all vaccine groups).
- Unsolicited adverse events leading to premature withdrawal from study (from day 1 to end of study for all vaccine groups).
- Unsolicited adverse events leading to dose reduction, interruption or delay in study vaccination (from day 1 to end of study for all vaccine groups).
- Medically attended adverse events (from day 1 to end of study for all vaccine groups).

13.4 Combined Solicited and Unsolicited Adverse Events

A summary of subjects with all combined solicited (regardless of their duration; where erythema and induration are reported as any events with a diameter >= 1 mm) and unsolicited adverse events will be provided. Solicited adverse events will be coded by MedDRA. For clintrial.gov and EudraCT posting purposes, a summary of combined solicited and unsolicited non-serious adverse events will be produced by System Organ Class and according to occurrence of each event. A further differentiation of combined adverse events according to seriousness, severity, or relationship is not performed.

13.5 Clinical Safety Laboratory Investigations

Not Applicable.

13.6 Concomitant Medication

The frequencies and percentages of subjects reporting concomitant medications will be tabulated overall and by vaccine group. Medications (generic drug name) will be coded using the WHODRUG dictionary (see section 8.7 for definition).

14. INTERIM ANALYSIS

14.1 Interim Analysis

There are no planned interim analyses for this study.

14.1.1 Futility Analysis

Not Applicable.

15. DATA MONITORING COMMITTEES

No Data Monitoring Committee will be utilized in this study.

16. PEER REVIEW

Peer review of analyses should be performed in accordance with the applicable procedures for validation of SAS programs used in clinical data analysis (see BCDM-17).

The following analyses are identified in the PID as key analyses to be peer reviewed by a biostatistician independent from the study:

- Primary and second secondary immunogenicity.

The following programs are identified as key programs to be peer reviewed by a second SP:

- Exclusion file(s).

17. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

For the complete list of tables, listings and figures, please refer to the Table of Contents (TOC) stored in the eTMF. Note that a listing of individual immunogenicity lab data (see "Other TOC" tab in the TOC) will be created for each center, to allow data dissemination to the study subjects. This listing will show the following data:

- Subject ID
- Actual vaccine(s) received by the subject
- Lab results for immunogenicity at each visit.

This listing is mentioned in the tab "Other TOC" in the TOC and will not be part of the CSR stat package.

18. LAYOUT SPECIFICATIONS FOR TABLES, LISTINGS AND FIGURES

All TFL is to include the following header:

GSK Vaccines	Vaccine: Men ABCWY
Final Report: Study V102_15E1	Booster Dose in Healthy Adolescents

In all tables, listings and figures, vaccine groups will be labeled as

Study Group	**Study Label**
ABCWY_0_2	ABCWY_0_2
B_0_2	B_0_2
ABCWY_0_2_6	ABCWY_0_2_6
ABCWY_0_6	ABCWY_0_6
Naive_ABCWY	Naive_ABCWY
Naive_B	Naive_B

For the mock-up catalogue to be used during programming, please refer to the document stored in within the SAS Drug Development (SDD) server.

Since all TFLs will be produced using SAS®, the output actually generated may slightly differ from the mock-ups presented in the study specific Mock-up catalogue.

19. REFERENCES

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