Statistical Analysis Plan Amendment 3

Study ID: 217043

Official Title of Study: A Phase II, randomised, partially blinded study to assess the safety, tolerability and immunogenicity of meningococcal combined ABCWY vaccine when administered to healthy infants.

NCT number: NCT05082285

Date of Document: 13-Oct-2025

Information Type:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title:	A Phase II, randomised, partially blinded study to assess the safety, tolerability and immunogenicity of meningococcal combined ABCWY vaccine when administered to healthy infants.
Study Number:	217043
Compound Number:	GSK4023393A
Abbreviated Title:	MENACWY=MEN7B-003

Sponsor Name: GlaxoSmithKline Biologicals SA (GSK)

Regulatory Agency Identifier Number(s) Not Applicable

Registry	**ID**
EudraCT number	2021-001367-24
EU CT number	2023-506449-40-00

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TABLE OF CONTENTS

PAGE

TITLE PAGE 1

VERSION HISTORY 6

1. INTRODUCTION 8
   - 1.1. Objectives, Estimands and Endpoints 8
   - 1.2. Study Design 9

2. STATISTICAL HYPOTHESES 13
   - 2.1. Multiplicity Adjustment 13

3. ANALYSIS SETS 13
   - 3.1. Criteria for eliminating data from Analysis Sets 13

4. STATISTICAL ANALYSES 16
   - 4.1. General Considerations 16
     - 4.1.1. General Methodology 16
     - 4.1.2. Baseline Definition 16
   - 4.2. Primary Endpoint(s) Analyses 16
     - 4.2.1. Definition of endpoints 16
       - 4.2.1.1. Safety and reactogenicity 16
       - 4.2.1.2. Serogroup B indicator strains 17
       - 4.2.1.3. Serogroups A, C, W and Y 17
     - 4.2.2. Main analytical approach 18
     - 4.2.3. Sensitivity analyses 18
   - 4.3. Interim Analyses 18
   - 4.4. Changes to Protocol Defined Analyses 18

5. SAMPLE SIZE DETERMINATION 19

6. SUPPORTING DOCUMENTATION 20
   - 6.1. Appendix 1 Study Population Analyses 20
     - 6.1.1. Participant Disposition 20
     - 6.1.2. Demographic and Baseline Characteristics 21
     - 6.1.3. Protocol Deviations 21
     - 6.1.4. Prior and Concomitant Medications 21
     - 6.1.5. Additional Analyses Due to the COVID-19 Pandemic 21
   - 6.2. Appendix 2 Electronic Clinical Outcome Assessment (eCOA) Compliance 21
     - 6.2.1. eDiary compliance 21
   - 6.3. Appendix 3 Data Derivations Rule 22
     - 6.3.1. Attributing events to vaccine doses 22
     - 6.3.2. Handling of Partial Dates 23
     - 6.3.3. Data derivation 23
       - 6.3.3.1. Age at vaccination in days 23
       - 6.3.3.2. Age at vaccination in months 23
       - 6.3.3.3. Weight 24
       - 6.3.3.4. Height 24
       - 6.3.3.5. Body mass index (BMI) 24

6.3.3.6. Temperature 24
6.3.3.7. Numerical serology results 24
6.3.3.8. Geometric mean titres (GMTs) and concentrations (GMCs) 25
6.3.3.9. Onset day 25
6.3.3.10. Duration of events 25
6.3.3.11. Counting rules for combining solicited and unsolicited adverse events 25
6.3.3.12. Counting rules for occurrences of solicited adverse events 25
6.3.4. Display of decimals 25
6.3.4.1. Percentages 25
6.3.4.2. Differences in percentages 26
6.3.4.3. Demographic/baseline characteristics statistics 26
6.3.4.4. Serological summary statistics 27
6.3.5. Statistical methodology 27
6.3.5.1. Exact confidence intervals around proportions 27
6.3.5.2. Standardized asymptotic confidence intervals around differences in proportions 27

7. REFERENCES 28

LIST OF TABLES

PAGE

Table 1 Study objectives, endpoints and estimands 8
Table 2 Study groups, intervention and blinding 12
Table 3 List of elimination criteria 13
Table 4 LOD, LLOQ and ULOQ values 19
Table 5 Assumptions, sample sizes and power 20

LIST OF FIGURES

PAGE

Figure 1 Study design overview 11

VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	24 September 2021	Amendment 1 (01 September 2021)	Not Applicable	Original version
SAP Amendment 1	09 November 2023	Amendment 3 (31 October 2022)	• Section 1.2 added [redacted] • Section 3.1 removed references to elimination codes and added elimination criteria rules for all analysis sets • Section 4.3 revision of interim analysis strategy • Section 5 updated sample size calculations and assumptions	• New testing strategy implemented • Alignment with current PD management processes • Interim analysis performed on complete/final data, therefore no independent statistical support group is needed • Alignment with Protocol Amendment 3 and with changes in the testing scheme
SAP Amendment 2	17 July 2024	Amendment 4 (28 February 2024)	• Table 3 updated to track exclusions from analysis sets • Section 4.2.1.1 updated to track handling	• Exclusions from FAS and PPS were clarified • Safety analysis clarification • Alignment with eCOA

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			strategy for duplicate AEs • Section 6.2 added eDiary compliance analysis • Section 6.3.3.10 updated Solicited AEs duration definition	compliance expectations • Alignment with current expectations
SAP Amendment 3	13 Oct 2025	Amendment 4 (28 February 2024)	• Section 4.4 updated to include 4-fold analysis and LOD, LLOQ and ULOQ values	• Alignment with current expectations

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the CSR for Study 217043. Details of the planned interim analysis, as well as the final analyses, are provided.

1.1. Objectives, Estimands and Endpoints

Table 1 Study objectives, endpoints and estimands

Objectives	Endpoint(s) and estimand(s)
Primary	
• To evaluate the safety and reactogenicity of the MenACWY-7B vaccine ([redacted]), the MenABCWY vaccine, the MenB vaccine and the MenACWY-TT vaccine.	• The number and percentages of participants with solicited administration site events during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 301. • The number and percentages of participants with solicited systemic events during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 301. • The number and percentages of participants with any unsolicited adverse events (AEs) (including all medically attended adverse events [MAEs], serious adverse events [SAEs], AEs leading to withdrawal, and adverse events of special interest [AESIs]) during the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 301. • The number and percentages of participants with MAEs, SAEs, AEs leading to withdrawal and AESIs throughout the study period in all groups (Day 1 through Day 481).
• To assess the immune response to the MenACWY-7B vaccine ([redacted]), to the MenABCWY vaccine and to the MenB vaccine against all serogroup B indicator strains*.	• The percentages of participants with human serum bactericidal assay (hSBA) titers ≥ lower limit of quantitation (LLOQ) for each serogroup B indicator strain at: – 1 month after the second vaccination (Day 91) – pre-third vaccination (Day 301) – 1 month after the third vaccination (Day 331) • hSBA geometric mean titers (GMTs) for each serogroup B indicator strain at: – 1 month after the second vaccination (Day 91) – pre-third vaccination (Day 301) – 1 month after the third vaccination (Day 331). • hSBA geometric mean ratios (GMRs) for each serogroup B indicator strain at 1 month after the third vaccination (Day 331) compared to pre-third vaccination (Day 301).
• To assess the immune response to the MenACWY-7B vaccine ([redacted]), to the MenABCWY vaccine and to the MenACWY-TT vaccine against serogroups A, C, W and Y.	• The percentages of participants with hSBA titers ≥ LLOQ for each A, C, W and Y serogroup at: – 1 month after the second vaccination (Day 91) – pre-third vaccination (Day 301) – 1 month after the third vaccination (Day 331). • hSBA GMTs for each A, C, W and Y serogroup at: – 1 month after the second vaccination (Day 91) – pre-third vaccination (Day 301) – 1 month after the third vaccination (Day 331).

Objectives	Endpoint(s) and estimand(s)
	• hSBA GMRs for each A, C, W and Y serogroup at 1 month after the third vaccination (Day 331) compared to pre-third vaccination (Day 301).

*Immune response will be assessed using hSBAs against *Neisseria meningitidis (N. meningitidis)* CCI
CCI
CCI
CCI
CCI
CCI

1.2. Study Design

This is a Phase II, randomised, partially blinded, multi-country, self-contained study comprising of 2 parts designed to ensure the safety of participants (see Figure 1).

Part I of the study will include 4 study groups (2 groups in Step 1 and 2 groups in Step 2, randomised 3:1 in both steps) enrolled with a staggered approach (20 participants in Step 1 followed by 20 participants in Step 2) for a total of 40 participants (Figure 1).

The administration of the second vaccination in Step 1 and the enrolment in Step 2 will start only after a positive outcome following the Independent Data Monitoring Committee (IDMC) review of the safety data from participants receiving first dose in Step 1 (for details regarding safety assessment, please refer to Protocol Section 8).

Step 1:

- **ACWY-7B**CCI: Participants will receive 3 doses of the MenACWY-7B CCI vaccine at 2, 4 and 12 MoA.
- **MenB+MenACWY-TT:** Participants will receive 3 doses of both MenB and MenACWY-TT vaccines at 2, 4 and 12 MoA, as control for the ACWY-7B CCI group.

Step 2:

- **ACWY-7B**CCI: Participants will receive 3 doses of the MenACWY-7B CCI vaccine at 2, 4 and 12 MoA.
- **MenB+MenACWY-TT:** Participants will receive 3 doses of both MenB and MenACWY-TT vaccines at 2, 4 and 12 MoA, as control for the ACWY-7B CCI group.

Part II will start only after a positive outcome following IDMC review of the safety data from participants receiving the first dose of both lower-dosage (MenACWY-7B CCI) and higher-dosage (MenACWY-7B CCI) vaccine formulations in Part I of the study (see Protocol Section 8 for details on IDMC reviews).

In Part II, 648 eligible participants will be randomly assigned to 4 study groups in a 1:1:1:1 ratio:

- **ABCWY**: Participants will receive 3 doses of the MenABCWY vaccine at 2, 4 and 12 MoA.
- **ACWY-7B[redacted]**: Participants will receive 3 doses of the MenACWY-7B[redacted] vaccine at 2, 4 and 12 MoA.
- **ACWY-7B[redacted]**: Participants will receive 3 doses of the MenACWY-7B[redacted] vaccine at 2, 4 and 12 MoA.
- **MenB+MenACWY-TT**: Participants will receive 3 doses of both MenB and MenACWY-TT vaccines at 2, 4 and 12 MoA.

Note: The following non-study vaccines will be concomitantly administered as routine practice at study visits: *Infanrix-Hexa* and *Prevenar 13* at 2, 4, 12 MoA and *Rotarix* at 2 and 4 MoA. For more detailed information on study groups and treatments administered, refer to Table 2.

Duration of the study: The intended duration of the study, per participant, is approximately 16 months.

Control: active comparator: MenB and MenACWY-TT vaccines will be administered as control at 2, 4 and 12 MoA.

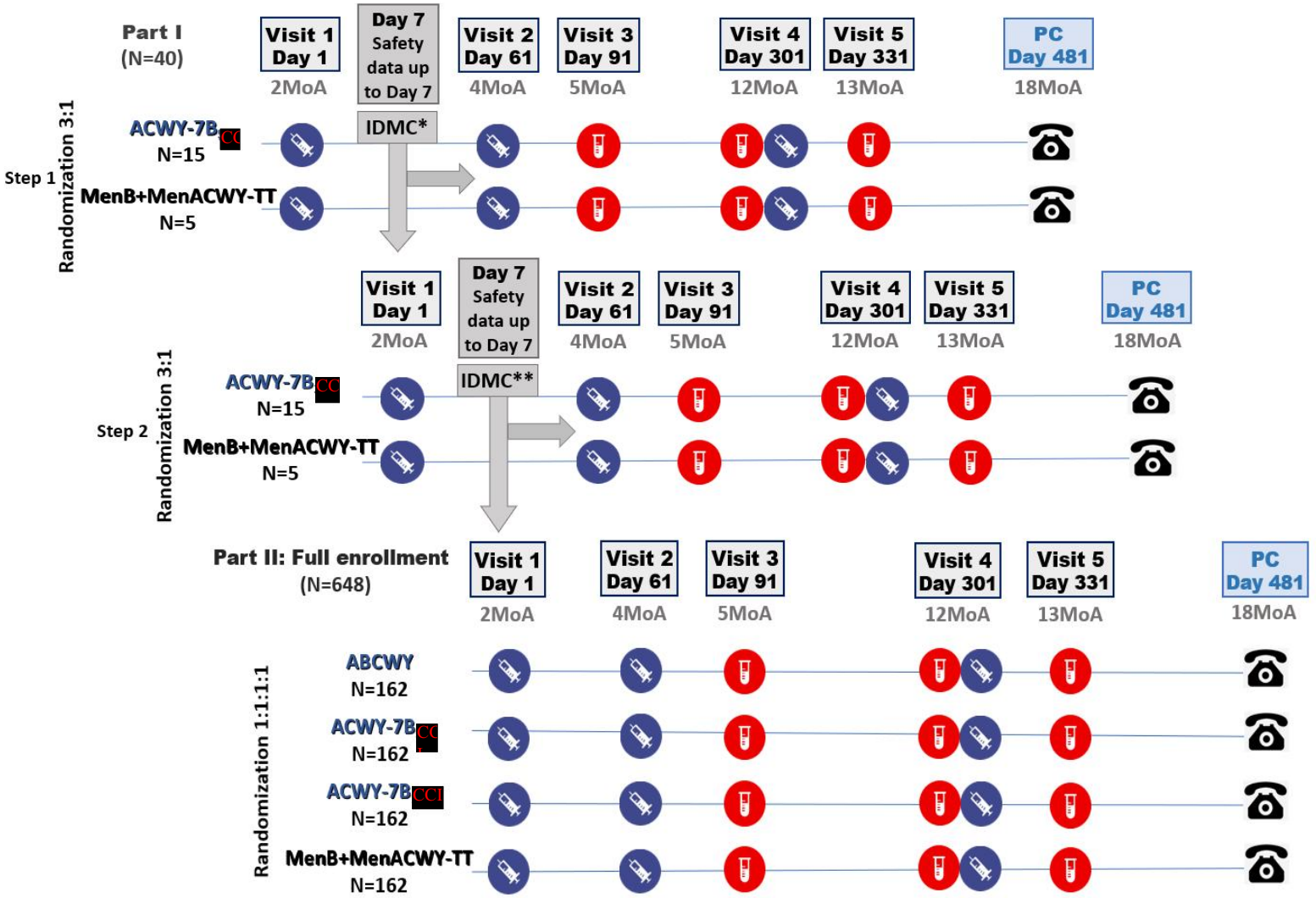
Blinding: partially blinding (refer to Protocol Section 6.3.5 for details on blinding and unblinding procedures).

Sampling schedule: Blood samples for immune response assessment will be collected from all participants at Visit 3 (Day 91), Visit 4 (Day 301) and Visit 5 (Day 331).

The **primary completion date** for the study is the Day 481 Phone Contact. Refer to Protocol Section 9.4.2 for the planned interim analysis.

[redacted]

Figure 1 Study design overview



Abbreviation: N, number of participants; IDMC, Independent Data Monitoring Committee.

 blood sampling;  study intervention administration;  phone call

* In Step 1, the IDMC will evaluate safety data up to Day 7 from all participants from ACWY-7B[redacted] and MenB+MenACWY-TT groups (15 and 5 participants per group, respectively). If favourable outcome, the enrolment in ACWY-7B[redacted] and MenB+MenACWY-TT groups will start (Step 2) and the administration of the second vaccination will take place in groups ACWY-7B[redacted] and MenB+MenACWY-TT.

** In Step 2, the IDMC will evaluate safety data up to Day 7 from all participants from ACWY-7B[redacted] and MenB+MenACWY-TT groups (15 and 5 participants per group, respectively). If favourable outcome, the full enrolment will start (Part 2) and the administration of the second vaccination will take place in ACWY-7B[redacted] and MenB+MenACWY-TT groups.

Note 1: This figure represents the main aspects of the study design. Refer to Protocol Table 1, Schedule of Activities, for details on all visits and contacts.

Note 2: For details regarding study groups, blinding and intervention administered within the study refer to Table 2.

Table 2 Study groups, intervention and blinding

Study groups	Number of participants	Age	Study interventions	Blinding	
				Part 1	Part 2
ABCWY	162	2 Months	MenABCWY	-	Observer-blinded
ACWY-7B[redacted]	177*		MenACWY-7B[redacted]	Open label	Observer-blinded
ACWY-7B[redacted]	177*		MenACWY-7B[redacted]	Open label	Observer-blinded
MenB+MenACWY-TT	172*		rMenB+OMV NZ	Open label	Open label
			MenACWY-TT		

* Groups ACWY-7B[redacted], ACWY-7B[redacted] and MenB+MenACWY-TT include the participants enrolled in both parts of the study.

Note: The following vaccines will be concomitantly administered as routine practice: Infanrix-Hexa and Prevenar 13 at 2, 4, 12 MoA and Rotarix at 2 and 4 MoA.

2. STATISTICAL HYPOTHESES

There are no statistical hypotheses to be tested. The study is descriptive.

2.1. Multiplicity Adjustment

Not applicable.

3. ANALYSIS SETS

Analysis set	Description
Enrolled Set	Participants who were randomised or received study intervention.
Exposed Set (ES)	All participants who received at least 1 dose of the study intervention. Analysis per group using the enrolled set is based on the administered intervention. Safety analysis in this study will be assessed using the ES.
Full Analysis Set (FAS)	All participants who received at least 1 dose of the study intervention and have post-vaccination immunogenicity data for at least one blood draw. The allocation in a group is done in function of the randomised intervention.
Per Protocol Set (PPS)	All participants from FAS minus participants with protocol deviations that lead to exclusions from PPS.

3.1. Criteria for eliminating data from Analysis Sets

The following criteria will be used to identify participants to be eliminated from analysis. Details are provided below (see Table 3) for exposed, full analysis and per protocol sets.

Table 3 List of elimination criteria

Protocol Deviation Category	Protocol Deviation Sub-Category	Timepoints where the criteria are checked	Applicable for analysis set/endpoint		
			ES	FAS	PPS*
Informed consent	a. Signed informed consent/assent not available on site	All	All	All	All
	b. Wrong informed consent/assent version signed	All	All	All	All
	c. Informed consent/assent not signed and/or dated by subject (parent/Legally Acceptable representative, if applicable)	All	All	All	All
	d. Informed consent/assent not signed and/or dated by appropriate site staff	All	All	All	All

Protocol Deviation Category	Protocol Deviation Sub-Category	Timepoints where the criteria are checked	Applicable for analysis set/endpoint		
			ES	FAS	PPS*
	e. Informed consent/assent not signed prior to any study procedure	All	All	All	All
Eligibility criteria	a. Eligibility criteria not met	All	None	None	All
Not withdrawn after developing withdrawal criteria	a. Not withdrawn from study	Visit 1	None	None	All
		Visit 2	None	None	Visit 2 onwards
		Visit 3	None	None	Visit 3 onwards
		Visit 4	None	None	Visit 4 onwards
		Visit 5	None	None	Visit 5
Excluded medication, vaccine or device	a. Medication, excluded by the protocol, was administered	Visit 1	None	None	All
		Visit 2	None	None	Visit 2 onwards
		Visit 3	None	None	Visit 3 onwards
		Visit 4	None	None	Visit 4 onwards
		Visit 5	None	None	Visit 5
	b. Vaccine, excluded by the protocol, was administered	Visit 1	None	None	All
		Visit 2	None	None	Visit 2 onwards
		Visit 3	None	None	Visit 3 onwards
		Visit 4	None	None	Visit 4 onwards
		Visit 5	None	None	Visit 5
Assessment or time point completion	a. Missed assessment	Visit 3	None	Exclusion applicable only if all assessments are missing	Visit 3
		Visit 4	None		Visit 4
		Visit 5	None		Visit 5
	d. Out of window assessment	Visit 3	None	None	Visit 3
		Visit 4	None	None	Visit 4
		Visit 5	None	None	Visit 5
	g. Out of window treatment administration	Visit 2	None	None	Visit 2 onwards
		Visit 4	None	None	Visit 4 onwards
Wrong study treatment/administration/dose	a. Study treatment not administered per protocol (except incomplete treatment course before treatment withdrawal and study treatment not administered at all)	Visit 1	None	None	All
		Visit 2	None	None	Visit 2 onwards
		Visit 4	None	None	Visit 4 onwards
	a. Study treatment not administered per protocol (Incomplete treatment course before treatment withdrawal)	Visit 2	Visit 2	None	Visit 2 onwards
		Visit 4	Visit 4	None	Visit 4 onwards
	a. Study treatment not administered per protocol (study treatment not administered at all)	Visit 1	All	All	All

Protocol Deviation Category	Protocol Deviation Sub-Category	Timepoints where the criteria are checked	Applicable for analysis set/endpoint		
			ES	FAS	PPS*
	b. Study treatment administered while contraindication	Visit 1	None	None	All
		Visit 2	None	None	Visit 2 onwards
		Visit 4	None	None	Visit 4 onwards
	c. Wrong study treatment or assignment administered	Visit 1	None	None	All
		Visit 2	None	None	Visit 2 onwards
		Visit 4	None	None	Visit 4 onwards
	d. Expired study treatment administered	Visit 1	None	None	All
		Visit 2	None	None	Visit 2 onwards
		Visit 4	None	None	Visit 4 onwards
	e. Use of study treatment impacted by a temperature excursion which was not reported or approved, or which was disapproved for further use	Visit 1	None	None	All
		Visit 2	None	None	Visit 2 onwards
		Visit 4	None	None	Visit 4 onwards
	f. Study treatment not prepared as per protocol (e.g., reconstitution)	Visit 1	None	None	All
		Visit 2	None	None	Visit 2 onwards
		Visit 4	None	None	Visit 4 onwards
Study procedures	a. Randomization procedures (e.g., subject assigned to wrong stratum, subject randomized out of order) - (if captured in another category do not capture here)	Visit 1	None	None	All
	b. Study blinding/unblinding procedures	Visit 1	None	None	All
		Visit 2	None	None	Visit 2 onwards
		Visit 4	None	None	Visit 4 onwards
	g. Biological sample specimen procedures	Visit 3	None	Exclusion applicable only if all samples are missing	Visit 3
		Visit 4	None		Visit 4
		Visit 5	None		Visit 5

ES = Exposed Set; FAS = Full Analysis Set; PPS = Per Protocol Set

* Subjects will be excluded from the PPS (global) if they are excluded at least at one timepoint from the PPS at visit level.

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

Participants who withdraw from the study will not be replaced.

In the case of wrong arm assigned at the time of randomization, for immunogenicity, analyses will be performed based on the assigned arm, whereas for safety, analyses will be performed based on the actual administered arm.

Confidence intervals will use 90% confidence levels unless otherwise specified.

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation (std), median, minimum and maximum. Categorical data will be summarized as the number and percentage of participants in each category.

4.1.2. Baseline Definition

Not applicable since no blood draw is performed before the first vaccination.

4.2. Primary Endpoint(s) Analyses

The analysis for the immunogenicity primary endpoint will be based on the FAS. The analysis will be repeated on the PPS, if the difference between FAS and PPS is >10%.

The analysis for the safety endpoints will be performed on the ES.

4.2.1. Definition of endpoints

4.2.1.1. Safety and reactogenicity

Primary Endpoint	Statistical Analysis Methods
The number and percentages of participants with solicited administration site and systemic events during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 301.	**Analysis set:** ES **Statistical methods:** summarised descriptively, no testing will be performed
The frequencies and percentages of participants with any unsolicited AEs (including all MAEs, SAEs, AEs leading to withdrawal, and AESIs) during the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 301.	**Analysis set:** ES **Statistical methods:** summarised descriptively, no testing will be performed
The frequencies and percentages of participants with MAEs, SAEs, AEs leading to withdrawal and AESIs throughout the study period in all groups (Day 1 through Day 481).	**Analysis set:** ES **Statistical methods:** summarised descriptively, no testing will be performed

In the event of duplicate solicited AEs being reported both in the study eCRF and the eDiary, the Investigator's assessment will be prioritized for the main analysis.

For participants who have more than one solicited local (i.e., injection site pain, erythema, swelling, induration) or systemic (i.e., fever [temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) measurement on a day, all data is listed. For the analysis, the worst measurement is analyzed. For example, if for a participant a temperature of 38.5°C and 39.0°C is recorded on one day, both values are listed, for the analysis the 39.0°C is analyzed.

4.2.1.2. Serogroup B indicator strains

Primary Endpoint	Statistical Analysis Methods
The percentages of participants with hSBA titer ≥LLOQ for each serogroup B indicator strain at 1 month after the second vaccination (Day 91), at pre-third vaccination (Day 301), and at 1 month after the third vaccination (Day 331).	**Analysis set:** FAS **Statistical methods:** The percentages of participants with hSBA titer ≥ LLOQ and the corresponding exact 2-sided 95% CIs based on the Clopper-Pearson method [Clopper, 1934] will be calculated for each serogroup B indicator strain. Difference between arms will be constructed with the method of Miettinen-Nurminen [Miettinen, 1985].
Summary statistics of hSBA titers and GMTs for each serogroup B indicator strain at 1 month after the second vaccination (Day 91), at pre-third vaccination (Day 301), and at 1 month after the third vaccination (Day 331).	**Analysis set:** FAS **Statistical methods:** For each serogroup B indicator strain 90% CIs for the GMTs ratio between ACWY-7B[redacted]/ ACWY-7B[redacted] and MenB, will be created by exponentiating (base 10) the least squares means and the lower and upper limits of the 90% CIs of the log transformed titers (base 10) obtained from a 2-way Analysis of Variance (ANOVA) with factors for arms and centre.
GMRs for each serogroup B indicator strain at 1 month after the third vaccination (Day 331) versus pre-third vaccination (Day 301).	**Analysis set:** FAS **Statistical methods:** hSBA GMRs for each serogroup B indicator strain at 1 month after the third vaccination (Day 331) versus pre-third vaccination (Day 301) will be analysed similarly as the GMTs ratio, where the outcome in the model is the log transformed titer ratio of Day 331 versus Day 301. 90% CIs for the GMRs ratio between ACWY-7B[redacted]/ ACWY-7B[redacted] and MenB, will be created by exponentiating (base 10) the least squares means and the lower and upper limits of the 90% CIs of the log transformed titers ratio (base 10) obtained from a 2-way ANOVA with factors for arms and centre.

4.2.1.3. Serogroups A, C, W and Y

Primary Endpoint	Statistical Analysis Methods
The percentages of participants with hSBA titer ≥ LLOQ for each A, C, W and Y serogroup at 1 month after the second vaccination (Day 91), at pre-third vaccination (Day 301), and at 1 month after the third vaccination (Day 331).	**Analysis set:** FAS **Statistical methods:** The percentages of participants with hSBA titer ≥ LLOQ and the corresponding exact 2-sided 95% CIs based on the Clopper-Pearson method [Clopper, 1934] will be calculated for each A, C, W, and Y serogroup. Difference between arms will be constructed with the method of Miettinen-Nurminen [Miettinen, 1985].
Summary statistics of hSBA titers and GMTs for each A, C, W and Y serogroup at 1 month after the second vaccination (Day 91), at	**Analysis set:** FAS **Statistical methods:**For each A, C, W, and Y serogroup 90% CIs for the GMTs ratio between ACWY-7B[redacted]/ ACWY-7B[redacted] and MenACWY-TT, will be created by exponentiating (base 10) the least squares means and the lower

Primary Endpoint	Statistical Analysis Methods
pre-third vaccination (Day 301), and at 1 month after the third vaccination (Day 331).	and upper limits of the 90% CIs of the log transformed titers (base 10) obtained from a 2-way ANOVA with factors for arms and centre.
GMRs for each A, C, W and Y serogroup at 1 month after the third vaccination (Day 331) versus pre-third vaccination (Day 301).	**Analysis set:** FAS **Statistical methods:** hSBA GMRs for each A, C, W, and Y serogroup at 1 month after the third vaccination (Day 331) versus pre-third vaccination (Day 301) will be analysed similarly as the GMTs ratio, where the outcome in the model is the log transformed titer ratio of Day 331 versus Day 301. 90% CIs for the GMRs ratio between ACWY-7B[redacted]/ ACWY-7B[redacted] and MenACWY-TT, will be created by exponentiating (base 10) the least squares means and the lower and upper limits of the 90% CIs of the log transformed titers ratio (base 10) obtained from a 2-way ANOVA with factors for arms and centre.

4.2.2. Main analytical approach

See Section 4.2.1.1 above Section 4.2.1.2, and Section 4.2.1.3.

4.2.3. Sensitivity analyses

Not applicable.

4.3. Interim Analyses

An interim safety and immunogenicity analysis will be performed when all participants had their blood drawn 1 month after the second vaccination (Day 91) and all immunogenicity results will be obtained. Data of participants of both part I and part II will be included. The interim analysis will be conducted such that the ongoing study integrity is maintained. Individual and interim analysis results will not be shared with investigators nor participants before the final database lock. The study team will receive analysis results by treatment group but no individual subject data.

Since some treatment groups of specific participants may be revealed during the interim analysis, the study will be considered single-blind for these participants from this point onwards, with the Investigator, site staff and participants remaining blinded up to EoS.

4.4. Changes to Protocol Defined Analyses

For each study group, the percentages of participants with 4-fold increase in hSBA titers at 1 month after the third vaccination (Day 331) versus pre-third vaccination (Day 301), and the corresponding exact 2-sided 95% CIs based on the Clopper-Pearson method [Clopper, 1934] will be calculated for each serogroup B indicator strain and each A, C, W and Y serogroup. Difference between arms will be constructed with the method of Miettinen-Nurminen [Miettinen, 1985].

The 4-fold rise in hSBA titers is defined as:

- a post-vaccination hSBA titer ≥4 times the LOD or ≥LLOQ, whichever is greater, for subjects with a pre-vaccination hSBA titer <LOD,

- a post-vaccination hSBA titer ≥4 times the LLOQ for subjects with a pre-vaccination hSBA titer ≥LOD but <LLOQ, and
- a post-vaccination hSBA titer ≥4 times the pre-vaccination titer for subjects with a pre-vaccination hSBA titer ≥LLOQ.

This analysis will be based on the FAS and it will be repeated on the PPS, if the difference between FAS and PPS is >10%.

The following table contains the LOD, LLOQ and ULOQ values to be used.

Table 4 LOD, LLOQ and ULOQ values

Serogroups / B strains	LOD*	LLOQ*	ULOQ*
A	5	12	4295
C	4	8	54828
W	4	8	10057
Y	4	10	7624
fHbp1.1	4	12	1369
NadA	4	8	7369
NHBA	4	7	3755
PorA	4	5	3775
fHbp Var1.13	4	7	2781
fHbp Var 2	4	5	1263
fHbp Var 3	4	4	2209

*Strain, assay cut-off(s) and unit(s) might be subject to change during the study (e.g., in case of requalification, revalidation or standardization). In this case, this will be documented either in a protocol amendment or in the clinical report.

5. SAMPLE SIZE DETERMINATION

The sample size determination was done to provide 90% CIs for the GMTs ratio between ACWY-7B[redacted]/ ACWY-7B[redacted] and MenB+MenACWY-TT at 1 month post second dose, that have enough power to be greater than 0.5 for the endpoints related to serogroups A, C, W and Y and serogroup B indicator strains and greater than 1 for the endpoint related to serogroup B indicator strains for additional fHbp antigens.

Table 5 reads the assumptions for standard deviation (SD) and expected GMTs ratio, sample sizes, and power.

The assumptions made are:

- 85% evaluable participants of/in Part I
- all 205 enrolled participants in Part II before study hold are non-evaluable, and
- 85% evaluable participants in Part II after study restart with 443 participants to be enrolled.

CCI



Participants who withdraw from the study will not be replaced.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

Unless otherwise specified, the study population analyses will be based on the FAS. A summary of the number of participants in each of the participant level analysis set will be provided.

6.1.1. Participant Disposition

A summary of the number and percentage of participants who completed the study as well as those who prematurely withdrew from the study will be provided. Reasons for study withdrawal will be summarized.

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics including age, gender, ethnicity, height/weight at screening and race will be summarized with descriptive statistics, based on the Enrolled Analysis Set.

Medical/vaccination history, pre-existing conditions, signs and/or symptoms present prior to the first dose of study intervention will be summarized respectively.

6.1.3. Protocol Deviations

Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations (where possible without knowing the study intervention details) are captured and categorised in the protocol deviations dataset.

Important (for example, those leading to exclusion from the analyses) protocol deviations will be summarized.

The number of participants enrolled into the study as well as the number of participants excluded from each analysis set will be tabulated.

6.1.4. Prior and Concomitant Medications

Concomitant medications will be coded using WHO Drug dictionary.

The number and percentage of participants using concomitant medications (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) at any point during Visit 1 to Visit 5 will be summarized.

6.1.5. Additional Analyses Due to the COVID-19 Pandemic

A participant is defined as having a suspected, probable or confirmed COVID-19 infection during the study if the answer is “Confirmed”, “Probable” or “Suspected” to the case diagnosis question from the COVID-19 coronavirus infection assessment eCRF. Numbers of participants with a suspected, probable or confirmed COVID-19 infection, and of COVID-19 test results will be summarized.

6.2. Appendix 2 Electronic Clinical Outcome Assessment (eCOA) Compliance

6.2.1. eDiary compliance

The study protocol defines a 7-day solicited AE follow-up period. eDiary compliance will be analyzed as follows:

- Overall eDiary compliance (Day 1 to 7) is calculated as

$$\frac{Total\ number\ of\ complete\ daily\ eDiaries}{Expected\ number\ of\ complete\ daily\ eDiaries} \times 100$$

  An eDiary is considered complete for a given day if there is no missing data within that day. For each subject the percentage of eDiary entries during the 7-day solicited period will be calculated and listed by visit. The average of the percentages of eDiary entries calculated at subject level will be reported by visit and overall, for each study group.

Monitoring of eDiary compliance will be done as follows:

eDiary compliance targets are defined based on quality tolerance limits (QTLs) that are reviewed on a regular basis. These QTLs are based on a different metric than the one used for the analysis and reported above, and no other compliance target was set for the study.

Based on QTL definition:

- An overall (Day 1 to 7) eDiary compliance at visit level around 80% is considered acceptable, i.e., at each visit at least 80% of subjects are compliant.
- A participant is considered compliant with eDiary at each visit if at least 70% of their daily eDiaries are complete (have no missing data), i.e., a participant is eDiary compliant at each visit if they meet the following criteria:

$$\frac{Total\ number\ of\ complete\ daily\ eDiaries}{Expected\ number\ of\ complete\ daily\ eDiaries} \times 100 \geq 70\%$$

6.3. Appendix 3 Data Derivations Rule

This section contains standard rules for data display and derivation for clinical and epidemiological studies.

6.3.1. Attributing events to vaccine doses

The dose relative to an event is the most recent study dose given to a participant prior to the start of a given event. For example, if the start date of an adverse event is between Dose 1 and Dose 2, the relative dose will be Dose 1.

If an event starts on the same day as a study dose, the relative dose will be derived from the additional information provided in the CRF using the contents of the flag indicating if the event occurred before or after vaccination. If ‘after vaccination’ is selected, the relative dose for the event will be the one administered on the start day of the event. If ‘before vaccination’ is selected, the relative dose for the event will be the dose prior to this one.

6.3.2. Handling of Partial Dates

When partially completed dates (i.e. with missing day or month) are used in calculations, the following standard rules will be applied:

- A missing day will be replaced by 15th
- A missing day and month will be replaced by June 30th

The following exceptions apply:

- Adverse event start dates with missing day:
  - If the event starts in the same month as at least one of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first (or only) study dose given during that month. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that month.
- Adverse event start dates with missing day and month:
  - If the event starts in the same year as at least one of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first (or only) study dose given during that year. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that year.

All other cases of incomplete AE or concomitant medication/vaccination start date will follow the standard rules above.

6.3.3. Data derivation

6.3.3.1. Age at vaccination in days

When age at vaccination is to be displayed in days, it will be calculated as:

Age = date of vaccination minus date of birth

6.3.3.2. Age at vaccination in months

When age at vaccination is to be displayed in months, it will be calculated as the number of complete calendar months between the date of birth (DOB) and the date of vaccination. For example:

DOB = 10JUN2017, Date of vaccination = 09JUL2018 -> Age = 12 months

DOB = 10JUN2017, Date of vaccination = 10JUL2018 -> Age = 13 months

6.3.3.3. Weight

Weight will be presented in kilograms. Weights reported in pounds will be converted as follows:

Weight in kilograms = Weight in pounds / 2.2

6.3.3.4. Height

Height will be presented in centimeters. Heights reported in feet and inches will be converted as follows:

Height in centimeters = Height in inches x 2.54

6.3.3.5. Body mass index (BMI)

BMI will be calculated as follows:

BMI = (Weight in kilograms) / (Height in meters)^2

6.3.3.6. Temperature

Temperatures will be presented in degrees Celsius (°C). Temperatures reported in degrees Fahrenheit (°F) will be converted as follows:

Temperature (Celsius) = ((Temperature (Fahrenheit) - 32) x 5)/9

6.3.3.7. Numerical serology results

Numerical serology results will be derived from the content of IS.ISORRES in the SDTM dataset. For assays with a specific cut-off, the following derivation rules apply:

IS.ISORRES	**Derived value**
"NEG", "-", or "(-)"	cut-off/2
"POS", "+", or "(+)"	cut-off
"< value" and value is <= assay cut-off	cut-off/2
"< value" and value is > assay cut-off	value
"> value" and value is < assay cut-off	cut-off/2
"> value" and value is >= assay cut-off	value
"value" and value is < cut-off	cut-off/2
"value" and value is >= cut-off	value
All other cases	missing

6.3.3.8. Geometric mean titres (GMTs) and concentrations (GMCs)

Geometric Mean Titre (GMT) or Concentration (GMC) calculations are performed by taking the inverse logarithm of the mean of the log titre or concentration transformations. Antibody titres or concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off of the assay for the purpose of GMT/GMC calculation. The cut-off value is defined by the laboratory before the analysis and is described in the protocol.

6.3.3.9. Onset day

The onset day for an event (e.g. AE, medication, vaccination) is the number of days between the last study vaccination and the start date of the event. This is 1 for an event occurring on the same day as a vaccination (and reported as starting after vaccination).

6.3.3.10. Duration of events

The duration of an event with a start and end date will be the number of days between the start and end dates plus one day, i.e. an event that starts on 03MAR2018 and ends on 12MAR2018 has a duration of 10 days.

The duration of solicited adverse events is derived assuming that the solicited adverse event occurred continuously from the first day to the last day the event was reported, regardless of how many days the event was documented in between (i.e., *end date – start date + 1*).

6.3.3.11. Counting rules for combining solicited and unsolicited adverse events

For output combining solicited and unsolicited adverse events, all serious adverse events will be considered general events since the administration site flag is not included in the expedited adverse event CRF pages.

Multiple events with the same preferred term which start on the same day are counted as only one occurrence.

6.3.3.12. Counting rules for occurrences of solicited adverse events

When the occurrences of solicited adverse events are summarized, each event recorded as having occurred during a specific period will be counted as only one occurrence regardless of the number of days on which it occurs. Also, in the case of co-administered study vaccines, an injection site reaction recorded for a participant following multiple vaccines will be counted as only one occurrence.

6.3.4. Display of decimals

6.3.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with:

- no decimals when there are fewer than 50 participants in each tabulated group
- one decimal when there are at least 50 participants in at least one tabulated group
  - Exceptions will be made for percentages that are not 0% or 100% but appear as 0% or 100% due to rounding. For these specific cases the number of decimals will be increased until the displayed value is no longer 0% or 100%. Examples are given in the following table.

n/N	Displayed percentage
10/45	22%
1/45	2%
10/55	18.2%
1/55	1.8%
1/300	0.3%
1/3000	0.03%
1/30000	0.003%
299/300	99.7%
2999/3000	99.97%
29999/30000	99.997%

  - The display of additional decimals for values close to 0% or 100% will be applied only to point estimates and not confidence limits, which can be rounded and displayed as 0% or 100%.
  - Values of exactly 0% or 100% will be presented with no decimals regardless of the number of participants per tabulated group.

6.3.4.2. Differences in percentages

Differences in percentages and their corresponding confidence limits will be displayed with one more decimal than the maximum number used to display the individual percentages, for example the difference between two percentages displayed with one decimal will be displayed with two decimals.

6.3.4.3. Demographic/baseline characteristics statistics

The mean, median, and standard deviation for continuous baseline characteristics (height, weight, body mass index (BMI), pre-vaccination body temperature) will be presented with one decimal.

The minimum and maximum values and quartile values (if required) will be presented with the same number of decimals as the observed values.

The maxima and minima of transformed height variables will be displayed with no decimals.

The maxima and minima of transformed weight variables will be displayed with no decimals with the exception of values are below 10kg where one decimal will be displayed.

The maximum and minima of transformed body temperatures will be displayed with one decimal.

6.3.4.4. Serological summary statistics

The number of decimals used when displaying geometric mean titers (GMT) or concentrations (GMC) and their confidence limits is shown in the following table:

GMT or GMC value	Number of decimals to display
<0.1	3
>=0.1 and <10	2
>=10 and <1000	1
>=1000	0

When multiple categories of GMT or GMC values are present in the same table, the number of decimals displayed should match that of the smallest category (i.e. the one with the higher number of decimals). For example, if GMT or GMC values of <0.1 appear in the same table as values of >=0.1 and <10, 3 decimals should be displayed for both.

GMT or GMC ratios and their confidence limits will be displayed with 2 decimals regardless of the actual values.

6.3.5. Statistical methodology

6.3.5.1. Exact confidence intervals around proportions

The exact confidence intervals around within-group proportions are derived using the method of Clopper and Pearson [Clopper, 1934].

6.3.5.2. Standardized asymptotic confidence intervals around differences in proportions

The standardized asymptotic confidence intervals around differences in proportions are derived using the method of Miettinen and Nurminen [Miettinen, 1985].

7. REFERENCES

Clopper CJ, Pearson ES. The Use of Confidence or Fiducial Limits Illustrated in the case of the Binomial. *Biometrika*. 1934;26:404-413.

Miettinen, O. S. and Nurminen, M. Comparative analysis of two rates. *Statistics in Medicine*, 1985;4,213-226.