STATISTICAL ANALYSIS PLAN

Study Title:	A Phase IV, Open-Label, Multi-Center Study to Evaluate the Safety and the 1-year Persistence of Antibody Response Among Children Who Received 4 Doses of the Novartis MenACWY Conjugate Vaccine at 2, 4, 6 and 12 Months of Age in South Korea
Study Number:	V59_75
Protocol Version and Date:	1, 10 DEC 14
Phase of Development:	Phase 4
Sponsor:	Novartis Vaccines
Plan Prepared by:	PPD
Version and Date:	Version 1: Date (24 JUN 15)
Approvers:	PPD, Supervisory Biostatistician
	PPD, Cluster Head
	PPD, Cluster Physician
	PPD, Clinical Trial Leader
	PPD, Medical Writer

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LIST OF ABBREVIATIONS

AE	Adverse Event
BCDM	Biostatistics and Clinical Data Management
CSR	Clinical Study Report
cCTL	Central Clinical Trial Leader
DMC	Data Monitoring Committee
eTMF	Electronic Trial Master File
FAS	Full Analysis Set
GMT	Geometric Mean Titer
hSBA	Human Complement Serum Bactericidal Assay
ICH	International Conference on Harmonization
IM	Intramuscular
LQ	Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
PD	Protocol Deviation
PPS	Per Protocol Set
rSBA	Rabbit Complement Serum Bactericidal Assay
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBA	Serum Bactericidal Activity
SD	Standard Deviation
SDD	SAS Drug Development
SP	Statistical Programmer
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEMP	Template
TFL	Tables, Figures and Listings
TOC	Table of Content

1. BACKGROUND AND RATIONALE

The purpose/aim of this Phase IV multicenter open label study is to evaluate the safety and the persistence of the antibody response among children who received 4 doses of the MenACWY conjugate vaccine at 2, 4, 6 and 12 months of age in the republic of South Korea, as a post marketing commitment.

MenACWY (Menveo®) has been approved for use in South Korea, from 2 years up to 55 years of age. The indication was extended in May 2014 to infants 2 months of age to 55 years, and as post commitment of indication change, the Regulatory Authorities of the Republic of South Korea (MFDS) have requested data on immunogenicity persistence in the Korean children population who received 4 doses of Menveo® at 2, 4, 6 and 12 months of age.

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

2. OBJECTIVES

2.1 Primary Objective(s)

Primary Safety Objective(s)

To assess the safety and tolerability of MenACWY administered at 2, 4, 6 and12 months of age.

Primary Immunogenicity Objective(s)

1. To evaluate the persistence of the antibody response against *N. meningitidis* serogroups A, C, W and Y at approximately 1 year after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age) of MenACWY vaccine as measured by hSBA titers ≥8.

2. To evaluate the persistence of the antibody response against *N. meningitidis* serogroups A, C, W and Y at approximately 1 year after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age) of MenACWY vaccine as measured by rSBA titers ≥8 and ≥128.

2.2 Secondary Objective(s)

1. To describe hSBA titers ≥8 and hSBA GMTs against *N. meningitidis* serogroups A, C, W and Y 1 month after a full vaccination series at 2, 4, 6 and 12 months of age.

2. To describe rSBA titers ≥8 and ≥128 and rSBA GMTs against *N. meningitidis* serogroups A, C, W and Y 1 month after a full vaccination series at 2, 4, 6 and 12 months of age

3. To evaluate the persistence of the antibody response against *N. meningitidis* serogroups A, C, W and Y at approximately 1 year after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age) of MenACWY vaccine as measured by hSBA GMTs and rSBA GMTs.

3. STUDY DESIGN

This is a Phase IV multicenter open label study planned at 6 sites. The study design has 6 clinical visits. At the first 4 visits the subjects will receive a dose of MenACWY vaccine and at visit 5 and 6 a blood draw will be taken. The subjects study participation is approximately 22 months. See also Table 3-1 for an overview of the clinical visits and Table 3-2 for the time and events.

Table 3-1: Overview of the study design

Number of Subjects	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
	2-Months	4-Months	6-Months	12-Months	13- Months	24- Months
135	Menveo®	Menveo®	Menveo®	Menveo®	**Blood draw**	**Blood draw**

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

Table 3-*2*: Time and Events Table – Treatment Period

Visit Type		**Clinic Visit**	**Phone Call**	**Clinic Visit**	**Phone Call**	**Clinic Visit**	**Phone Call**	**Clinic Visit**	**Phone Call**	**Clinic Visit**	**Clinic Visit**
Study Day		**1**	**3**	**61**	**63**	**121**	**123**	**301**	**304**	**331**	**661**
Visit Window (Days)		**n/a**	**-1/+1**	**+/-7**	**n/a**	**+/-7**	**-1/+1**	**+14**	**-1/+1**	**-7/+14**	**+/-60**
Months of age		**2**		**4**		**6**		**12**		**13**	**24**
Visit Number		**1**		**2**		**3**		**4**		**5**	**6**
Study Event	**References to protocol**										
Study Treatment											
Vaccination	Section 5.2	X		X		X		X			
Screening and Safety											
Inform Consent *	Section 5.1.1	X[a]									
Medical History	Section 5.1.2	X									
Physical Exam	Section 5.1.2 and 5.3.1	X[b]		X		X		X		X	X
Exclusion/Inclusion Criteria	Section 4.0	X[c]		X		X		X		X	X
30 Minutes Post Injection Assessment	Section 5.2.1	X		X		X		X			
Subject Diary Dispensed/Training	Section 5.2.1	X		X		X		X			
Subject Diary Reminder Call	Section 5.2.2		X		X		X		X		
Subject Diary Review/ Collect	Section 5.3.1			X		X		X		X	
Assess all solicited AEs	Section 7.1.1 and 7.1.3			X[d]		X[d]		X[d]		X[d]	
Assess SAEs	Section 7.1.4			X[e]		X[e]		X[e]		X[e]	X[e]

Visit Type		**Clinic Visit**	**Phone Call**	**Clinic Visit**	**Phone Call**	**Clinic Visit**	**Phone Call**	**Clinic Visit**	**Phone Call**	**Clinic Visit**	**Clinic Visit**
Study Day		**1**	**3**	**61**	**63**	**121**	**123**	**301**	**304**	**331**	**661**
Visit Window (Days)		**n/a**	**-1/+1**	**+/-7**	**n/a**	**+/-7**	**-1/+1**	**+14**	**-1/+1**	**-7/+14**	**+/-60**
Months of age		**2**		**4**		**6**		**12**		**13**	**24**
Visit Number		**1**		**2**		**3**		**4**		**5**	**6**
Study Event	**References to protocol**										
Medically attended AEs, AEs leading to withdrawal	Section 7.1.4.1 and 7.1.3	~~X~~		X[c]		X[c]		X[c]		X[e]	X[e]
Immunogenicity											
Serology blood draw	Section 3.5.									X	X

Notes:

a. Confirm consent form(s) signed prior to any procedures; * May be collected up to 5 days prior to vaccination on day 1.
b. Physical examination must be performed by a qualified healthcare professional.
c. Procedures to be performed prior to vaccination.
d. Only solicited adverse event (AE) occurred during the day of each vaccination and for the following 6 days will be reported by the subject on a subject diary.
e. SAEs, medically attended AE and AEs leading to study or vaccine withdrawal will be collected through Day 661. Please see section 6.6 for greater detail regarding methods for SAE and AEs leading to study or vaccine withdrawal collection.

4. RANDOMIZATION AND BLINDING

4.1 Method of Group Assignment and Randomization

This is a non-randomized, single-arm study. Enrolled subjects will be manually assigned a unique Subject ID. The Subject ID will be the subject's unique identification number for all CRFs and associated study documentation that will be used for duration of the study.

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

4.1.1 Definition of 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

- Subjects got vaccinated with the correct vaccine but containing a lower volume

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

4.2 Blinding and Unblinding

Not Applicable.

5. SAMPLE SIZE AND POWER CONSIDERATIONS

A total of 135 subjects will be enrolled in this study. This will lead to an estimated 100 evaluable subjects after taking into account an approximately 25% drop-out rate. The sample size is based on the number of subjects requested and agreed upon with the South Korean Heath Authorities for this persistence study.

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 statistical co-reviewer verified and documented the sample size/power considerations. This document was completed prior to finalization of the protocol and stored in Enterprise/eTMF Repository/V59_75/Cluster Documents/Statistical analysis /Statistical Analysis Plan/Other.

For details please refer to section 8.5 of the protocol.

6. DETERMINATION OF PROTOCOL DEVIATIONS

6.1 Definition of Protocol Deviations

Clinical Study Report (CSR) reportable protocol deviations (PDs) 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.
  - Subject had contraindication for a subsequent study vaccination but was vaccinated.
  - Concomitant infection related to the vaccine which may influence immune response.
- Subject received wrong vaccine or incorrect dose
  - Study vaccine was not administered at all
  - Vaccine administration not according to protocol.
- Subject took an excluded concomitant medication
  - Administration of concomitant vaccine(s) forbidden in the protocol.
  - Administration of any medication forbidden by the protocol.
- Subject enrolled and did not satisfy the entry criteria
  - Subject did not meet entry criteria.
- Key study procedures missed or performed out of window
  - Subject did not comply with study vaccination schedule.
  - Subject did not provide any post-vaccination safety data.
  - Subject did not comply with blood draw schedule.
  - Serological results not available post-vaccination.
  - Obvious incoherence, abnormal serology evolution or error in data.

CSR reportable PD 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 center and overall and individual subject listings will be provided in an appendix.

Prior to the analysis, designated sponsor staff will develop a memo that describes the PDs that lead 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

Prior to the analysis, a set of listings will be provided to the Cluster Physician and the Clinical Trial Leader (CTL) for review according to SOP MON-11.

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

After the review, the Cluster Physician and the CTL will provide the Biostatistician with:

- An assessment of CSR reportable PD based on clinical data review.
- An assessment of subjects without PD (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: ≥ 450 mm Measurements < 0 mm
Induration	For subjects < 6 years: ≥ 250 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 vaccination status in the trial, and receive a subject ID.

7.2 Exposed Set

All subjects in the All Enrolled Set who receive at least one study vaccination.

7.3 Full Analysis Set (FAS), Immunogenicity Set

All subjects in the All Enrolled Set, who receive at least one study vaccination and provide in-treatment immunogenicity, will be included in the FAS analysis sets as defined below:

- FAS hSBA Visit 6, primary objective

  FAS population with subjects that have an evaluable hSBA Visit 6 assessment, one year after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age), for at least one serogroup
- FAS rSBA Visit 6, primary objective

  FAS population with subjects that have an evaluable rSBA Visit 6 assessment, one year after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age), for at least one serogroup
- FAS hSBA Visit 5, secondary objective

  FAS population with subjects that have an evaluable hSBA Visit 5 assessment, one month after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age), for at least one serogroup
- FAS rSBA Visit 5, secondary objective

  FAS population with subjects that have an evaluable rSBA Visit 5 assessment, one month after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age), for at least one serogroup

7.4 Per Protocol Set (PPS), Immunogenicity Set

All subjects in the FAS Immunogenicity set (FAS hSBAVisit5, FAS rSBAVisit5, FAS hSBA Visit 6 and FAS rSBA Visit 6) who:

- Correctly receive the vaccine (i.e., receive the vaccine and at the scheduled time points).
- Have no CSR reportable protocol deviations leading to exclusion (see section 6.2) as defined prior to analysis.
- Are not excluded due to other reasons defined prior to analysis (see section 6.2).

In case of vaccination error, the subject is excluded from the PPS.

If a subject received the correct study vaccine (dose, batch) but from another ongoing study at the site then the subject should be excluded from the PPS.

Similarly to the FAS, the PPS populations will be defined as:

- PPS hSBA Visit 6, primary objective

  PPS population with subjects that have an evaluable hSBA Visit 6 assessment, one year after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age), for at least one serogroup and have no CSR reportable protocol deviations at that time point

- PPS rSBA Visit 6, primary objective

  PPS population with subjects that have an evaluable rSBA Visit 6 assessment, one year after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age), for at least one serogroup and have no CSR reportable protocol deviations at that time point

- PPS hSBA Visit 5, secondary objective

  PPS population with subjects that have an evaluable hSBA Visit 5 assessment , one month after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age), for at least one serogroup and have no CSR reportable protocol deviations at that time point

- PPS rSBA Visit 5, secondary objective

  PPS population with subjects that have an evaluable rSBA Visit 5 assessment, one month after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age), for at least one serogroup and have no CSR reportable protocol deviations at that time point

7.5 Safety Set

Solicited Safety Set

The solicited adverse events safety set will be split into 4 periods of 7 days, following each vaccination (day 1-day 7, with day 1 the day of a vaccination) to collect the solicited adverse events after each vaccination separately. The Solicited Adverse Events Safety Set per vaccination consists of all subjects in the Exposed Set with any solicited adverse event data and/or indicators of solicited adverse events at:

- Visit 1 at planned day 1 (Solicited Safety Set Visit 1)
- Visit 2 at planned day 61 (Solicited Safety Set Visit 2)
- Visit 3 at planned day 121 (Solicited Safety Set Visit 3)
- Visit 4 at planned day 301 (Solicited Safety Set Visit 4)

Unsolicited Safety Set

The unsolicited adverse events safety set will be split into 4 periods, following each vaccination with duration until the next vaccination or study termination. The Unsolicited Adverse Events Safety Set consists of all subjects in the Exposed Set with any unsolicited adverse event data in the period of:

- Visit 1/day 1 to visit 2/day 61 (Unsolicited Safety Set Period 1)
- Visit 2/day 61 to visit 3/day 121 (Unsolicited Safety Set Period 2)
- Visit 3/day 121 to visit 4/day 301 (Unsolicited Safety Set Period 3)
- Visit 4/day 301 to visit 6/day 661 or study termination (Unsolicited Safety Set Period 4)
- Overall

Overall Safety Set

All subjects who are in the solicited safety set and/or in the unsolicited safety set.

Subjects providing only 30 minutes postvaccination safety data will be reported separately in a 30 minute postvaccination safety analysis and excluded from all other safety analysis.

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

There is no additional analysis set.

7.7 Overview of Analysis Sets by PD Code

Table 7.7-1: Unsolicited Safety Sets

PD code	PD Description	Study Objective/ Period	Safety Set, Unsolicited AEs, Period 1	Safety Set, Unsolicited AEs, Period 2	Safety Set, Unsolicited AEs, Period 3	Safety Set, Unsolicited AEs, Period 4	Safety Set, Unsolicited AEs, Overall
	Exclusion code		SSU10FL	SSU11FL	SSU12FL	SSU13FL	SSUFL
100	Study vaccine not administered AT ALL	All Study	EXC	EXC	EXC	EXC	EXC
115.1	Subject did not provide any post-vaccination unsolicited safety data in period 1	Visit 1/Day 1 to Visit 2/Day 61	EXC	None	None	None	None
115.2	Subject did not provide any post-vaccination unsolicited safety data in period 2	Visit 2/Day 61 to Visit 3/Day 121	None	EXC	None	None	None
115.3	Subject did not provide any post-vaccination unsolicited safety data in period 3	Visit 3/Day 121 to Visit 4/Day 301	None	None	EXC	None	None
115.4	Subject did not provide any post-vaccination unsolicited safety data in period 4	Visit 4/Day 301 to Visit 6/Day 661 or Study End	None	None	None	EXC	None

EXC = excluded from this analysis set; None=No exclusion;

.

Table 7.7-2: Exposed, Overall and Solicited Safety Sets

PD code	PD Description	Study Objective/ Period	All Exposed Set	Overall Safety Set	Safety Set, Solicited AEs, Period T6H*-D7	Safety Set, Solicited AEs, Period T6H*-D3	Safety Set, Solicited AEs, Period D4-D7	Safety Set, Solicited AEs, Period T30m*
	Exclusion code		EXPFL	SAFFL	SSS10FL	SSS11FL	SSS12FL	
100	Study vaccine not administered AT ALL	All Study	EXC	EXC	EXC	EXC	EXC	EXC
116.1	Subject did not provide any post-vaccination solicited safety data after vaccination 1	Day 1 through Day 7 after Vaccination 1	None	None	EXC	EXC	EXC	None
116.2	Subject did not provide any post-vaccination solicited safety data after vaccination 2	Day 1 through Day 7 after Vaccination 2	None	None	EXC	EXC	EXC	None
116.3	Subject did not provide any post-vaccination solicited safety data after vaccination 3	Day 1 through Day 7 after Vaccination 3	None	None	EXC	EXC	EXC	None
116.4	Subject did not provide any post-vaccination solicited safety data after vaccination 4	Day 1 through Day 7 after Vaccination 4	None	None	EXC	EXC	EXC	None

* T30m and T6H=Day 1 time points of 30 min and 6 hrs respectively following vaccination; EXC = excluded from this analysis set. None=No exclusion;

Table 7.7-3: Immunogenicity Sets

PD code	PD Description	Study Objective/ Period	All Exposed	FAS Visit 5	FAS Visit 6	PPS Visit 5	PPS Visit 6
	Exclusion code		EXPFL	FAS10FL	FAS11FL	PPS10FL	PPS11FL
100	Study vaccine not administered AT ALL	All Study	EXC	EXC	EXC	EXC	EXC
110.1	hSBA serological results are not available at Visit 5	Day 331	None	EXC	None	EXC	None
110.2	hSBA serological results are not available at Visit 6	Day 661	None	None	EXC	None	EXC
110.3	rSBA serological results are not available at Visit 5	Day 331	None	EXC	None	EXC	None
110.4	rSBA serological results are not available at Visit 6	Day 661	None	None	EXC	None	EXC
112.1	Obvious deviation from Laboratory Manual or error in laboratory data at Visit 5	Day 331	None	None	None	EXC	None
112.2	Obvious deviation from Laboratory Manual or error in laboratory data at Visit 6	Day 661	None	None	None	None	EXC
140	Vaccination not according to protocol	Day 1 through Day 301	None	None	None	EXC	EXC
140.2	Administration of expired vaccine	Day 1 through Day 301	None	None	None	EXC	EXC
140.3	Administration of lower volume of the study vaccine	Day 1 through Day 301	None	None	None	EXC	EXC
140.4	Incomplete vaccination series	Day 1 through Day 301	None	None	None	EXC	EXC

PD code	PD Description	Study Objective/ Period	All Exposed	FAS Visit 5	FAS Visit 6	PPS Visit 5	PPS Visit 6
	Exclusion code		EXPFL	FAS10FL	FAS11FL	PPS10FL	PPS11FL
150.1	Administration of forbidden vaccine	Before Visit 5 (Day 331)	None	None	None	EXC	EXC
150.2	Administration of forbidden vaccine	Before Visit 6 (Day 661) but After Visit 5 (Day 331)	None	None	None	None	EXC
200	Subject did not meet entry criteria	Day 1	None	None	None	EXC	EXC
220	Subject had contraindication for a subsequent study vaccination but was vaccinated	All Study	None	None	None	EXC	EXC
230.1	Administration of forbidden medication	Before Visit 5 (Day 331)	None	None	None	EXC	EXC
230.2	Administration of forbidden medication	Before Visit 6 (Day 661) but after Visit 5 (Day 331)	None	None	None	None	EXC
240	Underlying medical condition forbidden by the protocol	All Study	None	None	None	EXC	EXC
250.1	Concomitant infection related to the vaccine which may influence immune response	Before Visit 5 (Day 331)	None	None	None	EXC	EXC
250.2	Concomitant infection related to the vaccine which may influence immune response	Before Visit 6 (Day 661) but After Visit 5 (Day 331)	None	None	None	None	EXC

PD code	PD Description	Study Objective/ Period	All Exposed	FAS Visit 5	FAS Visit 6	PPS Visit 5	PPS Visit 6
	Exclusion code		EXPFL	FAS10FL	FAS11FL	PPS10FL	PPS11FL
260.2	Visit 2 vaccination performed out of planned visit window	Visit 2 (Day 61)	None	None	None	EXC	EXC
260.3	Visit 3 vaccination performed out of planned visit window	Visit 3 (Day 121)	None	None	None	EXC	EXC
260.4	Visit 4 vaccination performed out of planned visit window	Visit 4 (Day 301)	None	None	None	EXC	EXC
270.1	Visit 5 blood draw performed out of planned visit window	Visit 5 (Day 331)	None	None	None	EXC	None
270.2	Visit 6 blood draw performed out of planned visit window	Visit 6 (Day 661)	None	None	None	None	EXC

FAS = Full Analysis Set; PPS=Per Protocol Set; EXC = excluded from this analysis set; None=No exclusion;

8. GENERAL ISSUES FOR STATISTICAL ANALYSES

8.1 Adjustment for Covariates

Not applicable.

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 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

No imputation methods will be used to address missing values.

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 the FAS as the primary population and the PPS for sensitivity.

8.2.3 Efficacy Data

Not applicable.

8.3 Multicenter Studies

Center effects will be investigated by applying a ‘by center’ analysis, i.e., this analysis will be repeated for all centers to investigate if there is any heterogeneity between the participating centers.

8.4 Multiple Comparisons and Multiplicity

Not Applicable.

8.5 Immunogenicity/Safety/Other Subsets

Not applicable.

8.6 Subgroups

Analyses of the primary objectives will be repeated and stratified by center and by sex using the FAS. For details regarding the analyses by center please see section 8.3 above.

8.7 Derived and Computed Variables

Demographics

Age will be calculated in months, using the following formula:

(Date of Visit 1 – Date of Birth + 1) / 30.4

Body Mass Index (kg/m^2) will be calculated using the following formula:

Weight (kg) / Height^2 (m^2)

Immunogenicity

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

Titer greater or equal to a given threshold is defined as binary variable for non-missing values as:

= 1, if the titer is superior or equal to the given threshold

= 0, otherwise

Geometric Mean Titer

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.

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 first vaccination 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.

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

Safety Laboratory Data

Not applicable

Previous, 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.

8.8 Analysis Software

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

8.9 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 will be $\log_{10}$-transformed. GMTs and their 95% CIs are computed by exponentiating (base 10) the least squares means and 95% CIs of the $\log_{10}$ titers.

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 CSR reportable protocol deviations will also be presented.

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

10. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

10.1 Demographics

Age, height, weight and body mass index will be summarized by reporting the mean, standard deviation, median and range, and will be calculated by center and overall.

The frequencies and percentages of subjects by sex, ethnic origin, race will be presented by center and overall. Demographic data will be tabulated for the All Enrolled, FAS Visit 6 (primary population) and Safety sets.

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 center and overall. Medical history data will be tabulated for the All Enrolled, FAS Visit 6 and Safety sets.

11. IMMUNOGENICITY ANALYSIS

11.1 Blood Samples

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

11.2 Primary Objectives Analysis

Primary Immunogenicity Objective(s)

1. To evaluate the persistence of the antibody response against *N. meningitidis* serogroups A, C, W and Y at approximately 1 year after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age) of MenACWY vaccine as measured by hSBA titers ≥8.

2. To evaluate the persistence of the antibody response against *N. meningitidis* serogroups A, C, W and Y at approximately 1 year after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age) of MenACWY vaccine as measured by rSBA titers ≥8 and ≥128.

Primary hypotheses:

No statistical tests will be done.

Statistical models:

No statistical models will be applied.

Statistical methods:

Analysis of binary data

The primary objective of the study is the persistence one year after the complete schedule of 4 vaccinations, expressed as the number and percentage of subjects with a hSBA titer ≥ 8 or a rSBA titer ≥ 8 and ≥128 at Visit 6.

These percentages will be presented along with associated two-sided 95% Clopper-Pearson confidence intervals.

Handling of missing values for Immunogenicity Data

For immunogenicity data, it may be reasonable to consider missing immunogenicity values as missing completely at random (MCAR), i.e., not informative. Therefore, the

primary analysis will comprise a complete case analysis only, without introducing any bias. Imputation methods will not be used.

Titers below the limit of detection will be set to half that limit for the purposes of analysis.

11.3 Secondary Objectives Analysis

Secondary Objective(s)

1. To describe hSBA titers ≥8 and hSBA GMTs against N. meningitidis serogroups A, C, W and Y 1 month after a full vaccination series at 2, 4, 6 and 12 months of age.

2. To describe rSBA titers ≥8 and ≥128 and rSBA GMTs against N. meningitidis serogroups A, C, W and Y 1 month after a full vaccination series at 2, 4, 6 and 12 months of age

3. To evaluate the persistence of the antibody response against N. meningitidis serogroups A, C, W and Y at approximately 1 year after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age) of MenACWY vaccine as measured by hSBA GMTs and rSBA GMTs.

Secondary hypotheses:

No statistical tests will be done.

Statistical models:

No statistical models will be applied.

Statistical methods:

Log-normal distributed data

The statistical analyses will be performed on the logarithmically (base 10) transformed values. Individual titers below detection limit will be set to half that limit.

Geometric mean antibody titers (GMT) and GMRs:

The antibody titers will be summarized using GMTs with two-sided 95% confidence intervals. The calculation will be done by a proc univariate analysis. GMTs and 95% confidence intervals will be obtained by exponentiation (base 10) of the logarithmically transformed antibody titer and confidence limits. Moreover the geometric mean ratios (GMR) will be provided along with the 2-sided 95% confidence intervals. GMRs will be

calculated between visit 6 (one year after full vaccination) and visit 5 (one month after full vaccination).

Median, minimum, and maximum values will be obtained using original titer values.

Binary data

The evaluation at one month after the complete schedule of 4 vaccinations is expressed as the number and percentage of subjects with hSBA titer ≥ 8 or rSBA titer ≥ 8 and ≥128 at Visit 5.

These percentages will be presented along with associated two-sided 95% Clopper-Pearson confidence intervals.

11.4 Exploratory Objectives Analysis

Not Applicable.

12. EFFICACY ANALYSIS

12.1 Primary Objectives Analysis

12.2 Secondary Objectives Analysis

Not Applicable.

12.3 Exploratory Objectives Analysis

Not Applicable.

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. Data will be tabulated for the All Enrolled Set. (This corresponds to Table 14.1.1.5 in the TOC)

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 and collection method (i.e., clinical visit, postal mail, any means).
2. For each solicited adverse event, the frequencies of subjects with *valid data* will be presented by 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*, aggregated over time points: 30 min - day 7 will be divided into: 30 min, 6h - day 3, day 4 - day 7, and 6h - day 7.
4. For each solicited adverse event, the frequencies of subjects *with valid data*, aggregated over time points: 30 min - Day 7 will be divided into: 30 min, 6h - day 3, day 4 - day 7, and 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 diary card was present or not.

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). An overview of the collected solicited adverse events with severity indication is presented in Table 13.1.

Table 13.2-1: Overview of the Solicited Adverse Events with Severity Grading

	Reaction	Grade 0/None	Grade 1/Mild	Grade 2/Moderate	Grade 3/Severe
Local	Erythema	<10 mm	10-25 mm	26-50 mm	>50 mm
	Induration	<10 mm	10-25 mm	26-50 mm	>50 mm
	Tenderness	None	Minor light reaction to touch	Cried or protested to touch	Cried when injected limb was moved
Systemic	Change in eating habits	None	Eating less than normal for 1 - 2 feeds / meals	Missed 1 or 2 feeds / meals	Missed more than 2 feeds / meals
	Sleepiness	None	Shows an increased drowsiness	Sleeps through feeds / meals	Sleeps most of the time and it is hard to arouse him / her
	Irritability	None	Requires more cuddling and is less playful than usual	More difficult to settle	Unable to console
	Vomiting	None	1 - 2 times in 24 hours	3 - 5 times in 24 hours	6 or more times in 24 hours or requires intravenous hydration
	Diarrhea	Fewer than 2 loose stools in 24 hours	2 - 3 loose stools in 24 hours	4 - 5 loose stools in 24 hours	6 or more loose stools in 24 hours or requires intravenous hydration
	Fever	Captured as No (<38ºC) or Yes (≥38ºC)			

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 – day 7 and 6h - day 7, each without 30minutes 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 categorizations will be used to summarize the data for a pediatric population:

Type I: none (0 mm), any (1-9 mm, 10-25 mm, 26-50 mm, >50 mm)

Type II: Grade 0 (< 10 mm), any (10-25 mm, 26-50 mm, >50 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-<36.5, ≥36.5-<37.0, ≥37.0-<37.5, ≥37.5-<38.0, ≥38.0-<38.5, ≥38.5-<39.0, ≥39.0-<39.5, ≥39.5-<40.0, ≥40.0°C
- by 1.0 °C increments: <36.0, ≥36.0-<37.0, ≥37.0-<38.0, ≥ 38.0-<39.0, ≥39.0-<40, ≥40°C
- <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 an indicator of a systemic adverse event.

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

1. Daily reports of subjects with solicited adverse events.
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 – day 7, and 6h - day 7, each without 30 min).
4. Duration of solicited adverse events.
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- day 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).

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), 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(s) will be used: ≥ 1 mm, ≥ 10 mm. The summary will provide the frequencies and percentages of subjects with first onset of each solicited adverse events 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 and: ≥ 1 mm / ≥ 10, mm for erythema and induration. If a solicited adverse event continues beyond day 7 the period after day 7 is added.

The frequency distribution of the number of days will be provided in a summary table 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": ≥ 1 mm, ≥ 10 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 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 – day 7, 6h - day 7.

13.3 Unsolicited Adverse Events

The first-line analysis will use unsolicited adverse event data from all reporting sources combined. A second-line analysis will encompass the analysis of unsolicited adverse events by source (e.g. diary cards, medical records, study specific worksheet).

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, 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 summaries will be presented by onset and will include frequency distributions of the different adverse events:

- Vaccination period 1: Onset between visit 1/day 1 and visit 2/day 61.
- Vaccination period 2: Onset between visit 2/day 61 and visit 3/day 121.
- Vaccination period 3: Onset between visit 3/day 121 and visit 4/day 301.
- Vaccination period 4: Onset between visit 4/day 301 and visit 6/day 661or study termination.
- Overall

The analysis of unsolicited adverse events comprises the following categories:

- Medically attended unsolicited adverse event.
- Possibly or probably related medically attended unsolicited adverse events.
- Unsolicited adverse events leading to death.
- Serious adverse events.
- Possibly or probably related serious adverse event.
- Unsolicited adverse events leading to premature withdrawal from study.
- Unsolicited adverse events leading to dose reduction, interruption or delay in study vaccination.
- Unsolicited adverse events leading to hospitalization.

Solicited adverse events continuing beyond day 7 will be coded by MedDRA and combined with the respective unsolicited adverse events.

13.4 Combined Solicited and Unsolicited Adverse Events

A summary of subjects with all combined solicited (regardless of their duration) and unsolicited adverse events will be provided. Solicited adverse events will be coded by MedDRA. For clintrial.gov posting purposes, a summary of combined solicited and unsolicited non-serious adverse events will be produced. A further differentiation of combined adverse events according to seriousness, severity, or relationship is not possible.

13.5 Clinical Safety Laboratory Investigations

Not Applicable.

13.6 Concomitant Medication

The frequencies and percentages of subjects reporting concomitant medications will be tabulated. 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

Not Applicable

16. PEER REVIEW

The type of peer review required for each output is to be identified by the study Biostatistician and SP in the TOC (see BCDM-14 TEMP 04). Analyses/Outputs requiring statistical peer review correspond usually to the analyses of the primary and secondary objectives, and data conversion programs. Peer review of these analyses should be performed in accordance with the applicable procedures for validation of SAS programs used in clinical data analysis.

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

- Primary immunogenicity analysis.
- Secondary immunogenicity analyses

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

- Exclusion file(s).
- Data conversion program.

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 Enterprise/eTMF Repository/V59_75/Cluster Documents/Statistical analysis/Statistical analysis Plan.

18. LAYOUT SPECIFICATIONS FOR TABLES, LISTINGS AND FIGURES

All TFL is to include the following header:

Novartis Vaccines	Vaccine: MenACWY
Final Report: Study V59_75	Four Doses in Children 2 Month of Age

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

For the mock-up catalogue to be used during programming, please refer to the document stored in Home/analysis/V59/V59_75/final/prod/docs within the SAS Drug Development (SDD) server.

Since all TLFs 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

Nauta J. *Statistics in Clinical Vaccine Trials*. 2010. Heidelberg: Springer.

U.S. Department of Health and Human Services, Food and Drug Administration, CBER (2007): *Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials*

Clopper CJ, Pearson ES. *The use of confidential or fiducial limits illustrated in the case of the binomial*. Biometrika 1934; 26:404-413.

Novartis

Document Approval Certificate / PPD

The individuals listed have approved this document for implementation using an electronic signature in the Atlas EDMS. PPD

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STATISTICAL ANALYSIS PLAN

Study Title:	A Phase IV, Open-Label, Multi-Center Study to Evaluate the Safety and the 1-year Persistence of Antibody Response Among Children Who Received 4 Doses of the Novartis MenACWY Conjugate Vaccine at 2, 4, 6 and 12 Months of Age in South Korea
Study Number:	V59_75
Protocol Version and Date:	3, 26 FEB 2016
Phase of Development:	Phase 4
Sponsor:	GlaxoSmithKline
Plan Prepared by:	PPD
Version and Date:	Version 2: Date (07 JUN 16)
Approvers:	PPD, Director Biostatistics
	PPD, Cluster Head
	PPD, Cluster Physician
	PPD, Clinical Trial Leader
	PPD, Medical Writer

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
BCDM	Biostatistics and Clinical Data Management
CSR	Clinical Study Report
cCTL	Central Clinical Trial Leader
DMC	Data Monitoring Committee
eTMF	Electronic Trial Master File
FAS	Full Analysis Set
GMT	Geometric Mean Titer
hSBA	Human Complement Serum Bactericidal Assay
ICH	International Conference on Harmonization
IM	Intramuscular
LQ	Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
PD	Protocol Deviation
PPS	Per Protocol Set
rSBA	Rabbit Complement Serum Bactericidal Assay
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBA	Serum Bactericidal Activity
SD	Standard Deviation
SDD	SAS Drug Development
SP	Statistical Programmer
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEMP	Template
TFL	Tables, Figures and Listings
TOC	Table of Content

1. BACKGROUND AND RATIONALE

The purpose/aim of this Phase IV multicenter open label study is to evaluate the safety and the persistence of the antibody response among children who received 4 doses of the MenACWY conjugate vaccine at 2, 4, 6 and 12 months of age in the republic of South Korea, as a post marketing commitment.

MenACWY (Menveo®) has been approved for use in South Korea, from 2 years up to 55 years of age. The indication was extended in May 2014 to infants 2 months of age to 55 years, and as post commitment of indication change, the Regulatory Authorities of the Republic of South Korea (MFDS) have requested data on immunogenicity persistence in the Korean children population who received 4 doses of Menveo® at 2, 4, 6 and 12 months of age.

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

Reason for Analysis Plan update:

In protocol V3, the Time and Events table has been updated to be aligned with the protocol text that clinical visits need to be planned based on the previous visit and not based on a fixed time schedule. For this reason, a line with 'Days post Injection' has been added' to the table.

In protocol version 2, updates were made related to the change of the sponsor from Novartis vaccines to GlaxoSmithKline. This update did not trigger a SAP amendment. The sponsor name is updated in the current version of the SAP together with updates from protocol V3.

Some corrections were made in the protocol that does not affect the Statistical Analysis Plan.

Table 1-1 History of Protocol and SAP versions

Protocol Version	SAP version	Reason for SAP update/not update
V1, 10DEC 14	V1, 24JUN 15	Initial version
V2, 08 AUG 15		Update of protocol not triggering a SAP update
V3, 26 FEB 16	V2, 09 FEB 15	Time and Events Table updated

2. OBJECTIVES

2.1 Primary Objective(s)

Primary Safety Objective(s)

To assess the safety and tolerability of MenACWY administered at 2, 4, 6 and12 months of age.

Primary Immunogenicity Objective(s)

1. To evaluate the persistence of the antibody response against *N. meningitidis* serogroups A, C, W and Y at approximately 1 year after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age) of MenACWY vaccine as measured by hSBA titers ≥8.

2. To evaluate the persistence of the antibody response against *N. meningitidis* serogroups A, C, W and Y at approximately 1 year after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age) of MenACWY vaccine as measured by rSBA titers ≥8 and ≥128.

2.2 Secondary Objective(s)

1. To describe hSBA titers ≥8 and hSBA GMTs against *N. meningitidis* serogroups A, C, W and Y 1 month after a full vaccination series at 2, 4, 6 and 12 months of age.

2. To describe rSBA titers ≥8 and ≥128 and rSBA GMTs against *N. meningitidis* serogroups A, C, W and Y 1 month after a full vaccination series at 2, 4, 6 and 12 months of age

3. To evaluate the persistence of the antibody response against *N. meningitidis* serogroups A, C, W and Y at approximately 1 year after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age) of MenACWY vaccine as measured by hSBA GMTs and rSBA GMTs.

3. STUDY DESIGN

This is a Phase IV multicenter open label study planned at 6 sites. The study design has 6 clinical visits. At the first 4 visits the subjects will receive a dose of MenACWY vaccine and at visit 5 and 6 a blood draw will be taken. The subjects study participation is approximately 22 months. See also Table 3-1 for an overview of the clinical visits and Table 3-2 for the time and events.

Table 3-1: Overview of the study design

Number of Subjects	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
	2-Months	4-Months	6-Months	12-Months	13- Months	24- Months
135	Menveo®	Menveo®	Menveo®	Menveo®	**Blood draw**	**Blood draw**

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

Table 3-*2*: Time and Events Table – Treatment Period

Visit Type		Clinic Visit	Reminder Phone Call	Clinic Visit	Reminder Phone Call	Clinic Visit	Reminder Phone Call	Clinic Visit	Reminder Phone Call	Clinic Visit	Clinic Visit
Study Day		1	3	61	63	121	123	301	303	331	661
Days Post Injections			2 days post dose 1	60 days post dose 1	2 days post dose 2	60 days post dose 2	2 days post dose 3	180 days post dose 3	2 days post dose 4	30 days post dose 4	330 days post visit 5
Visit Window (Days)		n/a	-1/+1	+/-7	n/a	+/-7	-1/+1	+14	-1/+1	-7/+14	+/-60
Months of age		2		4		6		12		13	24
Visit Number		1		2		3		4		5	6
Study Event	**References**										
Study Treatment											
Vaccination	Section 5.2	X		X		X		X			
Screening and Safety											
Inform Consent *	Section 5.1.1	X[a]									
Medical History	Section 5.1.2	X									
Physical Exam	Section 5.1.2 and 5.3.1	X[b]		X		X		X		X	X
Exclusion/Inclusion Criteria	Section 4.0	X[c]		X		X		X		X	X
30 Minutes Post Injection Assessment	Section 5.2.1	X		X		X		X			
Subject Diary Dispensed/Training	Section 5.2.1	X		X		X		X			

Visit Type		**Clinic Visit**	**Reminder Phone Call**	**Clinic Visit**	**Reminder Phone Call**	**Clinic Visit**	**Reminder Phone Call**	**Clinic Visit**	**Reminder Phone Call**	**Clinic Visit**	**Clinic Visit**
Study Day		**1**	**3**	**61**	**63**	**121**	**123**	**301**	**303**	**331**	**661**
Days Post Injections			**2 days post dose 1**	**60 days post dose 1**	**2 days post dose 2**	**60 days post dose 2**	**2 days post dose 3**	**180 days post dose 3**	**2 days post dose 4**	**30 days post dose 4**	**330 days post visit 5**
Visit Window (Days)		**n/a**	**-1/+1**	**+/-7**	**n/a**	**+/-7**	**-1/+1**	**+14**	**-1/+1**	**-7/+14**	**+/-60**
Months of age		**2**		**4**		**6**		**12**		**13**	**24**
Visit Number		**1**		**2**		**3**		**4**		**5**	**6**
Study Event	**References**										
Subject Diary Reminder Call	Section 5.2.2		X		X		X		X		
Subject Diary Review/ Collect	Section 5.3.1			X		X		X		X	
Assess all solicited AEs	Section 7.1.1 and 7.1.3	X[d]		X[d]		X[d]		X[d]		X[d]	
Assess SAEs	Section 7.1.4	X[e]		X[e]		X[e]		X[e]		X[e]	X[e]
Medically attended AEs, AEs leading to withdrawal	Section 7.1.4.1 and 7.1.3	X[e]		X[e]		X[e]		X[e]		X[e]	X[e]
Immunogenicity											
Serology blood draw	Section 3.5.									X	X

Notes:

a. Confirm consent form(s) signed prior to any procedures. * May be collected up to 5 days prior to vaccination on day 1.

b. Physical examination must be performed by a qualified healthcare professional.
c. Procedures to be performed prior to vaccination.
d. Only solicited adverse event (AE) occurred during the day of each vaccination and for the following 6 days will be reported by the subject on a subject diary.
e. SAEs, medically attended AE and AEs leading to study or vaccine withdrawal will be collected through Day 661. Please see section 7.0 for greater detail regarding methods for SAE and AEs leading to study or vaccine withdrawal collection

4. RANDOMIZATION AND BLINDING

4.1 Method of Group Assignment and Randomization

This is a non-randomized, single-arm study. Enrolled subjects will be manually assigned a unique Subject ID. The Subject ID will be the subject's unique identification number for all CRFs and associated study documentation that will be used for duration of the study.

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

4.1.1 Definition of 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

▫ Subjects got vaccinated with the correct vaccine but containing a lower volume

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

4.2 Blinding and Unblinding

Not Applicable.

5. SAMPLE SIZE AND POWER CONSIDERATIONS

A total of 135 subjects will be enrolled in this study. This will lead to an estimated 100 evaluable subjects after taking into account an approximately 25% drop-out rate. The sample size is based on the number of subjects requested and agreed upon with the South Korean Heath Authorities for this persistence study.

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 statistical co-reviewer verified and documented the sample size/power considerations. This document was completed prior to finalization of the protocol and stored in Enterprise/eTMF Repository/V59_75/Cluster Documents/Statistical analysis /Statistical Analysis Plan/Other.

For details please refer to section 8.5 of the protocol.

6. DETERMINATION OF PROTOCOL DEVIATIONS

6.1 Definition of Protocol Deviations

Clinical Study Report (CSR) reportable protocol deviations (PDs) 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.
  - Subject had contraindication for a subsequent study vaccination but was vaccinated.
  - Concomitant infection related to the vaccine which may influence immune response.
- Subject received wrong vaccine or incorrect dose
  - Study vaccine was not administered at all
  - Vaccine administration not according to protocol.
- Subject took an excluded concomitant medication
  - Administration of concomitant vaccine(s) forbidden in the protocol.
  - Administration of any medication forbidden by the protocol.
- Subject enrolled and did not satisfy the entry criteria
  - Subject did not meet entry criteria.
- Key study procedures missed or performed out of window
  - Subject did not comply with study vaccination schedule.
  - Subject did not provide any post-vaccination safety data.
  - Subject did not comply with blood draw schedule.
  - Serological results not available post-vaccination.
  - Obvious incoherence, abnormal serology evolution or error in data.

CSR reportable PD 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 center and overall and individual subject listings will be provided in an appendix.

Prior to the analysis, designated sponsor staff will develop a memo that describes the PDs that lead 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

Prior to the analysis, a set of listings will be provided to the Cluster Physician and the Clinical Trial Leader (CTL) for review according to SOP MON-11.

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

After the review, the Cluster Physician and the CTL will provide the Biostatistician with:

- An assessment of CSR reportable PD based on clinical data review.
- An assessment of subjects without PD (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: ≥ 450 mm Measurements < 0 mm
Induration	For subjects < 6 years: ≥ 250 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 vaccination status in the trial, and receive a subject ID.

7.2 Exposed Set

All subjects in the All Enrolled Set who receive at least one study vaccination.

7.3 Full Analysis Set (FAS), Immunogenicity Set

All subjects in the All Enrolled Set, who receive at least one study vaccination and provide in-treatment immunogenicity, will be included in the FAS analysis sets as defined below:

- FAS hSBA Visit 6, primary objective

  FAS population with subjects that have an evaluable hSBA Visit 6 assessment, one year after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age), for at least one serogroup

- FAS rSBA Visit 6, primary objective

  FAS population with subjects that have an evaluable rSBA Visit 6 assessment, one year after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age), for at least one serogroup

- FAS hSBA Visit 5, secondary objective

  FAS population with subjects that have an evaluable hSBA Visit 5 assessment, one month after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age), for at least one serogroup

- FAS rSBA Visit 5, secondary objective

  FAS population with subjects that have an evaluable rSBA Visit 5 assessment, one month after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age), for at least one serogroup

7.4 Per Protocol Set (PPS), Immunogenicity Set

All subjects in the FAS Immunogenicity set (FAS hSBAVisit5, FAS rSBAVisit5, FAS hSBA Visit 6 and FAS rSBA Visit 6) who:

- Correctly receive the vaccine (i.e., receive the vaccine and at the scheduled time points).
- Have no CSR reportable protocol deviations leading to exclusion (see section 6.2) as defined prior to analysis.
- Are not excluded due to other reasons defined prior to analysis (see section 6.2).

In case of vaccination error, the subject is excluded from the PPS.

If a subject received the correct study vaccine (dose, batch) but from another ongoing study at the site then the subject should be excluded from the PPS.

Similarly to the FAS, the PPS populations will be defined as:

- PPS hSBA Visit 6, primary objective

  PPS population with subjects that have an evaluable hSBA Visit 6 assessment, one year after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age), for at least one serogroup and have no CSR reportable protocol deviations at that time point

- PPS rSBA Visit 6, primary objective

  PPS population with subjects that have an evaluable rSBA Visit 6 assessment, one year after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age), for at least one serogroup and have no CSR reportable protocol deviations at that time point

- PPS hSBA Visit 5, secondary objective

  PPS population with subjects that have an evaluable hSBA Visit 5 assessment , one month after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age), for at least one serogroup and have no CSR reportable protocol deviations at that time point

- PPS rSBA Visit 5, secondary objective

  PPS population with subjects that have an evaluable rSBA Visit 5 assessment, one month after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age), for at least one serogroup and have no CSR reportable protocol deviations at that time point

7.5 Safety Set

Solicited Safety Set

The solicited adverse events safety set will be split into 4 periods of 7 days, following each vaccination (day 1-day 7, with day 1 the day of a vaccination) to collect the solicited adverse events after each vaccination separately. The Solicited Adverse Events Safety Set per vaccination consists of all subjects in the Exposed Set with any solicited adverse event data and/or indicators of solicited adverse events at:

- Visit 1 at planned day 1 (Solicited Safety Set Visit 1)
- Visit 2 at planned day 61 (Solicited Safety Set Visit 2)
- Visit 3 at planned day 121 (Solicited Safety Set Visit 3)
- Visit 4 at planned day 301 (Solicited Safety Set Visit 4)

Unsolicited Safety Set

The unsolicited adverse events safety set will be split into 4 periods, following each vaccination with duration until the next vaccination or study termination. The Unsolicited Adverse Events Safety Set consists of all subjects in the Exposed Set with any unsolicited adverse event data in the period of:

- Visit 1/day 1 to visit 2/day 61 (Unsolicited Safety Set Period 1)
- Visit 2/day 61 to visit 3/day 121 (Unsolicited Safety Set Period 2)
- Visit 3/day 121 to visit 4/day 301 (Unsolicited Safety Set Period 3)
- Visit 4/day 301 to visit 6/day 661 or study termination (Unsolicited Safety Set Period 4)
- Overall

Overall Safety Set

All subjects who are in the solicited safety set and/or in the unsolicited safety set.

Subjects providing only 30 minutes postvaccination safety data will be reported separately in a 30 minute postvaccination safety analysis and excluded from all other safety analysis.

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

There is no additional analysis set.

7.7 Overview of Analysis Sets by PD Code

Table 7.7-1: Unsolicited Safety Sets

PD code	PD Description	Study Objective/ Period	Safety Set, Unsolicited AEs, Period 1	Safety Set, Unsolicited AEs, Period 2	Safety Set, Unsolicited AEs, Period 3	Safety Set, Unsolicited AEs, Period 4	Safety Set, Unsolicited AEs, Overall
	Exclusion code		SSU10FL	SSU11FL	SSU12FL	SSU13FL	SSUFL
100	Study vaccine not administered AT ALL	All Study	EXC	EXC	EXC	EXC	EXC
115.1	Subject did not provide any post-vaccination unsolicited safety data in period 1	Visit 1/Day 1 to Visit 2/Day 61	EXC	None	None	None	None
115.2	Subject did not provide any post-vaccination unsolicited safety data in period 2	Visit 2/Day 61 to Visit 3/Day 121	None	EXC	None	None	None
115.3	Subject did not provide any post-vaccination unsolicited safety data in period 3	Visit 3/Day 121 to Visit 4/Day 301	None	None	EXC	None	None
115.4	Subject did not provide any post-vaccination unsolicited safety data in period 4	Visit 4/Day 301 to Visit 6/Day 661 or Study End	None	None	None	EXC	None

EXC = excluded from this analysis set; None=No exclusion;

Table 7.7-2: Exposed, Overall and Solicited Safety Sets

PD code	PD Description	Study Objective/ Period	All Exposed Set	Overall Safety Set	Safety Set, Solicited AEs, Period T6H*-D7	Safety Set, Solicited AEs, Period T6H*-D3	Safety Set, Solicited AEs, Period D4-D7	Safety Set, Solicited AEs, Period T30m*
	Exclusion code		**EXPFL**	**SAFFL**	**SSS10FL**	**SSS11FL**	**SSS12FL**	
100	**Study vaccine not administered AT ALL**	**All Study**	EXC	EXC	EXC	EXC	EXC	EXC
116.1	**Subject did not provide any post-vaccination solicited safety data after vaccination 1**	**Day 1 through Day 7 after Vaccination 1**	None	None	EXC	EXC	EXC	None
116.2	**Subject did not provide any post-vaccination solicited safety data after vaccination 2**	**Day 1 through Day 7 after Vaccination 2**	None	None	EXC	EXC	EXC	None
116.3	**Subject did not provide any post-vaccination solicited safety data after vaccination 3**	**Day 1 through Day 7 after Vaccination 3**	None	None	EXC	EXC	EXC	None
116.4	**Subject did not provide any post-vaccination solicited safety data after vaccination 4**	**Day 1 through Day 7 after Vaccination 4**	None	None	EXC	EXC	EXC	None

* T30m and T6H=Day 1 time points of 30 min and 6 hrs respectively following vaccination; EXC = excluded from this analysis set. None=No exclusion;

Table 7.7-3: Immunogenicity Sets

PD code	PD Description	Study Objective/ Period	All Exposed	FAS Visit 5	FAS Visit 6	PPS Visit 5	PPS Visit 6
	Exclusion code		EXPFL	FAS10FL	FAS11FL	PPS10FL	PPS11FL
100	Study vaccine not administered AT ALL	All Study	EXC	EXC	EXC	EXC	EXC
110.1	hSBA serological results are not available at Visit 5	Day 331	None	EXC	None	EXC	None
110.2	hSBA serological results are not available at Visit 6	Day 661	None	None	EXC	None	EXC
110.3	rSBA serological results are not available at Visit 5	Day 331	None	EXC	None	EXC	None
110.4	rSBA serological results are not available at Visit 6	Day 661	None	None	EXC	None	EXC
112.1	Obvious deviation from Laboratory Manual or error in laboratory data at Visit 5	Day 331	None	None	None	EXC	None
112.2	Obvious deviation from Laboratory Manual or error in laboratory data at Visit 6	Day 661	None	None	None	None	EXC
140	Vaccination not according to protocol	Day 1 through Day 301	None	None	None	EXC	EXC
140.2	Administration of expired vaccine	Day 1 through Day 301	None	None	None	EXC	EXC
140.3	Administration of lower volume of the study vaccine	Day 1 through Day 301	None	None	None	EXC	EXC
140.4	Incomplete vaccination series	Day 1 through Day 301	None	None	None	EXC	EXC

PD code	PD Description	Study Objective/ Period	All Exposed	FAS Visit 5	FAS Visit 6	PPS Visit 5	PPS Visit 6
	Exclusion code		EXPFL	FAS10FL	FAS11FL	PPS10FL	PPS11FL
150.1	Administration of forbidden vaccine	Before Visit 5 (Day 331)	None	None	None	EXC	EXC
150.2	Administration of forbidden vaccine	Before Visit 6 (Day 661) but After Visit 5 (Day 331)	None	None	None	None	EXC
200	Subject did not meet entry criteria	Day 1	None	None	None	EXC	EXC
220	Subject had contraindication for a subsequent study vaccination but was vaccinated	All Study	None	None	None	EXC	EXC
230.1	Administration of forbidden medication	Before Visit 5 (Day 331)	None	None	None	EXC	EXC
230.2	Administration of forbidden medication	Before Visit 6 (Day 661) but after Visit 5 (Day 331)	None	None	None	None	EXC
240	Underlying medical condition forbidden by the protocol	All Study	None	None	None	EXC	EXC
250.1	Concomitant infection related to the vaccine which may influence immune response	Before Visit 5 (Day 331)	None	None	None	EXC	EXC
250.2	Concomitant infection related to the vaccine which may influence immune response	Before Visit 6 (Day 661) but After Visit 5 (Day 331)	None	None	None	None	EXC

PD code	PD Description	Study Objective/ Period	All Exposed	FAS Visit 5	FAS Visit 6	PPS Visit 5	PPS Visit 6
	Exclusion code		**EXPFL**	**FAS10FL**	**FAS11FL**	**PPS10FL**	**PPS11FL**
260.2	**Visit 2 vaccination performed out of planned visit window**	**Visit 2 (Day 61)**	None	None	None	EXC	EXC
260.3	**Visit 3 vaccination performed out of planned visit window**	**Visit 3 (Day 121)**	None	None	None	EXC	EXC
260.4	**Visit 4 vaccination performed out of planned visit window**	**Visit 4 (Day 301)**	None	None	None	EXC	EXC
270.1	**Visit 5 blood draw performed out of planned visit window**	**Visit 5 (Day 331)**	None	None	None	EXC	None
270.2	**Visit 6 blood draw performed out of planned visit window**	**Visit 6 (Day 661)**	None	None	None	None	EXC

FAS = Full Analysis Set; PPS=Per Protocol Set; EXC = excluded from this analysis set; None=No exclusion;

8. GENERAL ISSUES FOR STATISTICAL ANALYSES

8.1 Adjustment for Covariates

Not applicable.

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 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

No imputation methods will be used to address missing values.

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 the FAS as the primary population and the PPS for sensitivity.

8.2.3 Efficacy Data

Not applicable.

8.3 Multicenter Studies

Center effects will be investigated by applying a 'by center' analysis, i.e., this analysis will be repeated for all centers to investigate if there is any heterogeneity between the participating centers.

8.4 Multiple Comparisons and Multiplicity

Not Applicable.

8.5 Immunogenicity/Safety/Other Subsets

Not applicable.

8.6 Subgroups

Analyses of the primary objectives will be repeated and stratified by center and by sex using the FAS. For details regarding the analyses by center please see section 8.3 above.

8.7 Derived and Computed Variables

Demographics

Body Mass Index (kg/m^2) will be calculated using the following formula:

Weight (kg) / Height^2 (m^2)

Immunogenicity

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

Titer greater or equal to a given threshold is defined as binary variable for non-missing values as:

= 1, if the titer is superior or equal to the given threshold

= 0, otherwise

Geometric Mean Titer

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.

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 first vaccination 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.

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

Safety Laboratory Data

Not applicable

Previous, 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.

8.8 Analysis Software

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

8.9 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 will be $\log_{10}$-transformed. GMTs and their 95% CIs are computed by exponentiating (base 10) the least squares means and 95% CIs of the $\log_{10}$ titers.

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 CSR reportable protocol deviations will also be presented.

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

10. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

10.1 Demographics

Age, height, weight and body mass index will be summarized by reporting the mean, standard deviation, median and range, and will be calculated by center and overall.

The frequencies and percentages of subjects by sex, ethnic origin, race will be presented by center and overall. Demographic data will be tabulated for the All Enrolled, FAS Visit 6 (primary population) and Safety sets.

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 center and overall. Medical history data will be tabulated for the All Enrolled, FAS Visit 6 and Safety sets.

11. IMMUNOGENICITY ANALYSIS

11.1 Blood Samples

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

11.2 Primary Objectives Analysis

Primary Immunogenicity Objective(s)

1. To evaluate the persistence of the antibody response against *N. meningitidis* serogroups A, C, W and Y at approximately 1 year after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age) of MenACWY vaccine as measured by hSBA titers ≥8.

2. To evaluate the persistence of the antibody response against *N. meningitidis* serogroups A, C, W and Y at approximately 1 year after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age) of MenACWY vaccine as measured by rSBA titers ≥8 and ≥128.

Primary hypotheses:

No statistical tests will be done.

Statistical models:

No statistical models will be applied.

Statistical methods:

Analysis of binary data

The primary objective of the study is the persistence one year after the complete schedule of 4 vaccinations, expressed as the number and percentage of subjects with a hSBA titer ≥ 8 or a rSBA titer ≥ 8 and ≥128 at Visit 6.

These percentages will be presented along with associated two-sided 95% Clopper-Pearson confidence intervals.

Handling of missing values for Immunogenicity Data

For immunogenicity data, it may be reasonable to consider missing immunogenicity values as missing completely at random (MCAR), i.e., not informative. Therefore, the

primary analysis will comprise a complete case analysis only, without introducing any bias. Imputation methods will not be used.

Titers below the limit of detection will be set to half that limit for the purposes of analysis.

11.3 Secondary Objectives Analysis

Secondary Objective(s)

1. To describe hSBA titers ≥8 and hSBA GMTs against N. meningitidis serogroups A, C, W and Y 1 month after a full vaccination series at 2, 4, 6 and 12 months of age.

2. To describe rSBA titers ≥8 and ≥128 and rSBA GMTs against N. meningitidis serogroups A, C, W and Y 1 month after a full vaccination series at 2, 4, 6 and 12 months of age

3. To evaluate the persistence of the antibody response against N. meningitidis serogroups A, C, W and Y at approximately 1 year after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age) of MenACWY vaccine as measured by hSBA GMTs and rSBA GMTs.

Secondary hypotheses:

No statistical tests will be done.

Statistical models:

No statistical models will be applied.

Statistical methods:

Log-normal distributed data

The statistical analyses will be performed on the logarithmically (base 10) transformed values. Individual titers below detection limit will be set to half that limit.

Geometric mean antibody titers (GMT) and GMRs:

The antibody titers will be summarized using GMTs with two-sided 95% confidence intervals. The calculation will be done by a proc univariate analysis. GMTs and 95% confidence intervals will be obtained by exponentiation (base 10) of the logarithmically transformed antibody titer and confidence limits. Moreover the geometric mean ratios (GMR) will be provided along with the 2-sided 95% confidence intervals. GMRs will be

calculated between visit 6 (one year after full vaccination) and visit 5 (one month after full vaccination).

Median, minimum, and maximum values will be obtained using original titer values.

Binary data

The evaluation at one month after the complete schedule of 4 vaccinations is expressed as the number and percentage of subjects with hSBA titer ≥ 8 or rSBA titer ≥ 8 and ≥128 at Visit 5.

These percentages will be presented along with associated two-sided 95% Clopper-Pearson confidence intervals.

11.4 Exploratory Objectives Analysis

Not Applicable.

12. EFFICACY ANALYSIS

12.1 Primary Objectives Analysis

12.2 Secondary Objectives Analysis

Not Applicable.

12.3 Exploratory Objectives Analysis

Not Applicable.

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. Data will be tabulated for the All Enrolled Set. (This corresponds to Table 14.1.1.5 in the TOC)

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 and collection method (i.e., clinical visit, postal mail, any means).
2. For each solicited adverse event, the frequencies of subjects with *valid data* will be presented by 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*, aggregated over time points: 30 min - day 7 will be divided into: 30 min, 6h - day 3, day 4 - day 7, and 6h - day 7.
4. For each solicited adverse event, the frequencies of subjects *with valid data*, aggregated over time points: 30 min - Day 7 will be divided into: 30 min, 6h - day 3, day 4 - day 7, and 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 diary card was present or not.

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). An overview of the collected solicited adverse events with severity indication is presented in Table 13.1.

Table 13.2-1: Overview of the Solicited Adverse Events with Severity Grading

	Reaction	Grade 0/None	Grade 1/Mild	Grade 2/Moderate	Grade 3/Severe
Local	Erythema	<10 mm	10-25 mm	26-50 mm	>50 mm
	Induration	<10 mm	10-25 mm	26-50 mm	>50 mm
	Tenderness	None	Minor light reaction to touch	Cried or protested to touch	Cried when injected limb was moved
Systemic	Change in eating habits	None	Eating less than normal for 1 - 2 feeds / meals	Missed 1 or 2 feeds / meals	Missed more than 2 feeds / meals
	Sleepiness	None	Shows an increased drowsiness	Sleeps through feeds / meals	Sleeps most of the time and it is hard to arouse him / her
	Irritability	None	Requires more cuddling and is less playful than usual	More difficult to settle	Unable to console
	Vomiting	None	1 - 2 times in 24 hours	3 - 5 times in 24 hours	6 or more times in 24 hours or requires intravenous hydration
	Diarrhea	Fewer than 2 loose stools in 24 hours	2 - 3 loose stools in 24 hours	4 - 5 loose stools in 24 hours	6 or more loose stools in 24 hours or requires intravenous hydration
	Fever	Captured as No (<38ºC) or Yes (≥38ºC)			

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 – day 7 and 6h - day 7, each without 30minutes 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 categorizations will be used to summarize the data for a pediatric population:

Type I: none (0 mm), any (1-9 mm, 10-25 mm, 26-50 mm, >50 mm)

Type II: Grade 0 (< 10 mm), any (10-25 mm, 26-50 mm, >50 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-<36.5, ≥36.5-<37.0, ≥37.0-<37.5, ≥37.5-<38.0, ≥38.0-<38.5, ≥38.5-<39.0, ≥39.0-<39.5, ≥39.5-<40.0, ≥40.0°C
- by 1.0 °C increments: <36.0, ≥36.0-<37.0, ≥37.0-<38.0, ≥ 38.0-<39.0, ≥39.0-<40, ≥40°C
- <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 an indicator of a systemic adverse event.

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

1. Daily reports of subjects with solicited adverse events.
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 – day 7, and 6h - day 7, each without 30 min).
4. Duration of solicited adverse events.
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- day 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).

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), 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(s) will be used: ≥ 1 mm, ≥ 10 mm. The summary will provide the frequencies and percentages of subjects with first onset of each solicited adverse events 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 and: ≥ 1 mm / ≥ 10, mm for erythema and induration. If a solicited adverse event continues beyond day 7 the period after day 7 is added.

The frequency distribution of the number of days will be provided in a summary table 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": ≥ 1 mm, ≥ 10 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 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 – day 7, 6h - day 7.

13.3 Unsolicited Adverse Events

The first-line analysis will use unsolicited adverse event data from all reporting sources combined. A second-line analysis will encompass the analysis of unsolicited adverse events by source (e.g. diary cards, medical records, study specific worksheet).

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, 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 summaries will be presented by onset and will include frequency distributions of the different adverse events:

- Vaccination period 1: Onset between visit 1/day 1 and visit 2/day 61.
- Vaccination period 2: Onset between visit 2/day 61 and visit 3/day 121.
- Vaccination period 3: Onset between visit 3/day 121 and visit 4/day 301.
- Vaccination period 4: Onset between visit 4/day 301 and visit 6/day 661or study termination.
- Overall

The analysis of unsolicited adverse events comprises the following categories:

- Medically attended unsolicited adverse event.
- Possibly or probably related medically attended unsolicited adverse events.
- Unsolicited adverse events leading to death.
- Serious adverse events.
- Possibly or probably related serious adverse event.
- Unsolicited adverse events leading to premature withdrawal from study.
- Unsolicited adverse events leading to dose reduction, interruption or delay in study vaccination.
- Unsolicited adverse events leading to hospitalization.

Solicited adverse events continuing beyond day 7 will be coded by MedDRA and combined with the respective unsolicited adverse events.

13.4 Combined Solicited and Unsolicited Adverse Events

A summary of subjects with all combined solicited (regardless of their duration) and unsolicited adverse events will be provided. Solicited adverse events will be coded by MedDRA. For clintrial.gov posting purposes, a summary of combined solicited and unsolicited non-serious adverse events will be produced. A further differentiation of combined adverse events according to seriousness, severity, or relationship is not possible.

13.5 Clinical Safety Laboratory Investigations

Not Applicable.

13.6 Concomitant Medication

The frequencies and percentages of subjects reporting concomitant medications will be tabulated. 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

Not Applicable

16. PEER REVIEW

The type of peer review required for each output is to be identified by the study Biostatistician and SP in the TOC (see BCDM-14 TEMP 04). Analyses/Outputs requiring statistical peer review correspond usually to the analyses of the primary and secondary objectives, and data conversion programs. Peer review of these analyses should be performed in accordance with the applicable procedures for validation of SAS programs used in clinical data analysis.

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

- Primary immunogenicity analysis.
- Secondary immunogenicity analyses

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

- Exclusion file(s).
- Data conversion program.

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 Enterprise/eTMF Repository/V59_75/Cluster Documents/Statistical analysis/Statistical analysis Plan.

18. LAYOUT SPECIFICATIONS FOR TABLES, LISTINGS AND FIGURES

All TFL is to include the following header:

Novartis Vaccines	Vaccine: MenACWY
Final Report: Study V59_75	Four Doses in Children 2 Month of Age

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

For the mock-up catalogue to be used during programming, please refer to the document stored in Home/analysis/V59/V59_75/final/prod/docs within the SAS Drug Development (SDD) server.

Since all TLFs 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

Nauta J. *Statistics in Clinical Vaccine Trials*. 2010. Heidelberg: Springer.

U.S. Department of Health and Human Services, Food and Drug Administration, CBER (2007): *Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials*

Clopper CJ, Pearson ES. *The use of confidential or fiducial limits illustrated in the case of the binomial*. Biometrika 1934; 26:404-413.

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The individuals listed have approved this document for implementation using an electronic signature in the Atlas EDMS. / PPD

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STATISTICAL ANALYSIS PLAN AMENDMENT V59_75

Amendment Number 1

A Phase IV, Open-Label, Multi-Center Study to Evaluate the Safety and the 1-year Persistence of Antibody Response Among Children Who Received 4 Doses of the GSK MenACWY Conjugate Vaccine at 2, 4, 6 and 12 Months of Age in South Korea

The present amendment reflects changes to the Statistical Analysis Plan since the 1st version of the Statistical Analysis Plan.

DESCRIPTION OF CHANGE(S) AND RATIONALE:

In protocol version 3, mainly the Time and Events table has been updated to be aligned with the protocol text, to be sure that the clinical visits need to be planned based on the previous visit and not based on a fixed schedule. For this reason, a line with 'Days post Injection' has been added to the table.

Some corrections were made to the protocol that does not affect the Statistical Analysis Plan.

In protocol version 2, updates were made related to the change of the sponsor from Novartis Vaccines to GlaxoSmithKline. This update did not trigger a SAP amendment, but the update was made in this amendment.

CHANGE 1 *(Section 3, Table 3-2):*

Previously read:

Table 3-*2*: Time and Events Table – Treatment Period

Visit Type		Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit	Clinic Visit
Study Day		**1**	**3**	**61**	**63**	**121**	**123**	**301**	**304**	**331**	**661**
Visit Window (Days)		**n/a**	**-1/+1**	**+/-7**	**n/a**	**+/-7**	**-1/+1**	**+14**	**-1/+1**	**-7/+14**	**+/-60**
Months of age		**2**		**4**		**6**		**12**		**13**	**24**
Visit Number		**1**		**2**		**3**		**4**		**5**	**6**
Study Event	**References to protocol**										
Study Treatment											
Vaccination	Section 5.2	X		X		X		X			
Screening and Safety											
Inform Consent *	Section 5.1.1	X[a]									
Medical History	Section 5.1.2	X									
Physical Exam	Section 5.1.2 and 5.3.1	X[b]		X		X		X		X	X
Exclusion/Inclusion Criteria	Section 4.0	X[c]		X		X		X		X	X
30 Minutes Post Injection Assessment	Section 5.2.1	X		X		X		X			
Subject Diary Dispensed/Training	Section 5.2.1	X		X		X		X			
Subject Diary Reminder Call	Section 5.2.2		X		X		X		X		
Subject Diary Review/ Collect	Section 5.3.1			X		X		X		X	
Assess all solicited AEs	Section 7.1.1 and 7.1.3			X[d]		X[d]		X[d]		X[d]	

Visit Type		Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit	Clinic Visit
Study Day		**1**	**3**	**61**	**63**	**121**	**123**	**301**	**304**	**331**	**661**
Visit Window (Days)		**n/a**	**-1/+1**	**+/-7**	**n/a**	**+/-7**	**-1/+1**	**+14**	**-1/+1**	**-7/+14**	**+/-60**
Months of age		**2**		**4**		**6**		**12**		**13**	**24**
Visit Number		**1**		**2**		**3**		**4**		**5**	**6**
Study Event	**References to protocol**										
Assess SAEs	Section 7.1.4			X[e]		X[e]		X[e]		X[e]	X[e]
Medically attended AEs, AEs leading to withdrawal	Section 7.1.4.1 and 7.1.3	~~X~~		X[c]		X[c]		X[c]		X[e]	X[e]
Immunogenicity											
Serology blood draw	Section 3.5.									X	X

Notes:

a. Confirm consent form(s) signed prior to any procedures; * May be collected up to 5 days prior to vaccination on day 1.
b. Physical examination must be performed by a qualified healthcare professional.
c. Procedures to be performed prior to vaccination.
d. Only solicited adverse event (AE) occurred during the day of each vaccination and for the following 6 days will be reported by the subject on a subject diary.
e. SAEs, medically attended AE and AEs leading to study or vaccine withdrawal will be collected through Day 661. Please see section 6.6 for greater detail regarding methods for SAE and AEs leading to study or vaccine withdrawal collection.

Now Reads:

Table 3-*2*: Time and Events Table – Treatment Period

Visit Type		Clinic Visit	Reminder Phone Call	Clinic Visit	Reminder Phone Call	Clinic Visit	Reminder Phone Call	Clinic Visit	Reminder Phone Call	Clinic Visit	Clinic Visit
Study Day		1	3	61	63	121	123	301	303	331	661
Days Post Injections			2 days post dose 1	60 days post dose 1	2 days post dose 2	60 days post dose 2	2 days post dose 3	180 days post dose 3	2 days post dose 4	30 days post dose 4	330 days post visit 5
Visit Window (Days)		n/a	-1/+1	+/-7	n/a	+/-7	-1/+1	+14	-1/+1	-7/+14	+/-60
Months of age		2		4		6		12		13	24
Visit Number		1		2		3		4		5	6
Study Event	**References**										
Study Treatment											
Vaccination	Section 5.2	X		X		X		X			
Screening and Safety											
Inform Consent *	Section 5.1.1	X[a]									
Medical History	Section 5.1.2	X									
Physical Exam	Section 5.1.2 and 5.3.1	X[b]		X		X		X		X	X
Exclusion/Inclusion Criteria	Section 4.0	X[c]		X		X		X		X	X
30 Minutes Post Injection Assessment	Section 5.2.1	X		X		X		X			

Visit Type		Clinic Visit	Reminder Phone Call	Clinic Visit	Reminder Phone Call	Clinic Visit	Reminder Phone Call	Clinic Visit	Reminder Phone Call	Clinic Visit	Clinic Visit
Study Day		**1**	**3**	**61**	**63**	**121**	**123**	**301**	**303**	**331**	**661**
Days Post Injections			**2 days post dose 1**	**60 days post dose 1**	**2 days post dose 2**	**60 days post dose 2**	**2 days post dose 3**	**180 days post dose 3**	**2 days post dose 4**	**30 days post dose 4**	**330 days post visit 5**
Visit Window (Days)		**n/a**	**-1/+1**	**+/-7**	**n/a**	**+/-7**	**-1/+1**	**+14**	**-1/+1**	**-7/+14**	**+/-60**
Months of age		**2**		**4**		**6**		**12**		**13**	**24**
Visit Number		**1**		**2**		**3**		**4**		**5**	**6**
Study Event	**References**										
Subject Diary Dispensed/Training	Section 5.2.1	X		X		X		X			
Subject Diary Reminder Call	Section 5.2.2		X		X		X		X		
Subject Diary Review/ Collect	Section 5.3.1			X		X		X		X	
Assess all solicited AEs	Section 7.1.1 and 7.1.3	X[d]		X[d]		X[d]		X[d]		X[d]	
Assess SAEs	Section 7.1.4	X[e]		X[e]		X[e]		X[e]		X[e]	X[e]
Medically attended AEs, AEs leading to withdrawal	Section 7.1.4.1 and 7.1.3	X[e]		X[e]		X[e]		X[e]		X[e]	X[e]
Immunogenicity											

Visit Type		Clinic Visit	Reminder Phone Call	Clinic Visit	Reminder Phone Call	Clinic Visit	Reminder Phone Call	Clinic Visit	Reminder Phone Call	Clinic Visit	Clinic Visit
Study Day		**1**	**3**	**61**	**63**	**121**	**123**	**301**	**303**	**331**	**661**
Days Post Injections			**2 days post dose 1**	**60 days post dose 1**	**2 days post dose 2**	**60 days post dose 2**	**2 days post dose 3**	**180 days post dose 3**	**2 days post dose 4**	**30 days post dose 4**	**330 days post visit 5**
Visit Window (Days)		**n/a**	**-1/+1**	**+/-7**	**n/a**	**+/-7**	**-1/+1**	**+14**	**-1/+1**	**-7/+14**	**+/-60**
Months of age		**2**		**4**		**6**		**12**		**13**	**24**
Visit Number		**1**		**2**		**3**		**4**		**5**	**6**
Study Event	**References**										
Serology blood draw	Section 3.5.									X	X

Notes:

a. Confirm consent form(s) signed prior to any procedures. * May be collected up to 5 days prior to vaccination on day 1.
b. Physical examination must be performed by a qualified healthcare professional.
c. Procedures to be performed prior to vaccination.
d. Only solicited adverse event (AE) occurred during the day of each vaccination and for the following 6 days will be reported by the subject on a subject diary.
e. SAEs, medically attended AE and AEs leading to study or vaccine withdrawal will be collected through Day 661. Please see section 7.0 for greater detail regarding methods for SAE and AEs leading to study or vaccine withdrawal collection

Rationale for Change:

Protocol was updated with a new Time and Events Table, to clarify into more detail how the subsequent clinical visits need to be planned, not on a fixed schedule, but based on the previous visit.

CHANGE 2 *(Section 8, Chapter 8.7, line 1):*

Previously read:

Demographics

Age will be calculated in months, using the following formula:

(Date of Visit 1 – Date of Birth + 1) / 30.4

Body Mass Index (kg/m^2) will be calculated using the following formula:

Weight (kg) / Height^2 (m^2)

Now reads:

Body Mass Index (kg/m^2) will be calculated using the following formula:

Weight (kg) / Height^2 (m^2)

Rationale for Change:

All appropriate dates, birth date and study start date are known and SAS can calculate the age exact, which makes the approximation not applicable.

CHANGE 3 *(Throughout the Analysis Plan):*

Previously read:

Novartis Vaccines

Now reads:

GlaxoSmithKline Biologicals

Rationale for Change:

Sponsor name change

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