NCT04368429

STATISTICAL ANALYSIS PLAN

Protocol title:	**Immunogenicity and Safety of a Single Dose of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Children, Adolescents, and Adults 2 to 55 Years of Age**
Protocol number:	**EFC16335_MEQ00068**
Compound number (INN/Trademark):	**SP0047**
Study phase:	**III**
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VERSION HISTORY

This statistical analysis plan (SAP) for study EFC16335_MEQ00068 is based on the protocol dated 10-Mar-2020. There are no major changes to the statistical analysis features in this SAP. The first subject was randomized on 22-May-2020.

Table 1 - Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1.0	27-Nov-2020	Not Applicable	Original version

1 INTRODUCTION

1.1 STUDY DESIGN

This will be a Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center study to evaluate immune non-inferiority of MenACYW conjugate vaccine versus Menactra® and describe the safety and immunogenicity of the study vaccines in children (2-9 years of age), adolescents (10-17 years of age) and adults (18-55 years of age) in Japan. Approximately 360 healthy children, adolescents and adults will be stratified and randomly assigned in a 1:1 ratio to the following groups:

- Group 1(investigational): MenACYW conjugate vaccine (180 subjects)
- Group 2(control): Menactra® (180 subjects)

All subjects will provide blood samples for immunogenicity assessment at baseline (pre-vaccination) and at 30 days post-vaccination. Solicited injection site and systemic reactions will be collected for 7 days after vaccination, unsolicited adverse events (AEs) will be collected from Visit 1 (Day [D] 0) to Visit 2 (D30 [+14 days]), and serious adverse events (SAEs) will be collected from signing of the informed consent at D0 through D30 (+14 days) after vaccination.

Study primary analysis will be conducted after study completion.

1.2 OBJECTIVE AND ENDPOINTS

Table 2 - Objectives and endpoints

	Objectives	Endpoints
Primary	**To demonstrate the non-inferiority of the antibody responses to meningococcal serogroups A, C, Y, and W following the administration of a single dose of MenACYW conjugate vaccine compared with those observed following the administration of a single dose Menactra®**	**Vaccine seroresponse of meningococcal serogroups A, C, Y, and W measured by serum bactericidal assay using human complement (hSBA) assessed at baseline (Visit 1, D0, before vaccination) and at Visit 2 (D30[+14 days]) after vaccination for immune noninferiority between MenACYW conjugate vaccine and Menactra® (Group 1 versus Group 2)**
Secondary	**Immunogenicity** • To describe the antibody responses to the meningococcal serogroups A, C, Y, and W before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Menactra®	Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA assessed at baseline (D0, before vaccination) and after vaccination at D30 (+14 days) for all groups • hSBA vaccine seroresponse • Proportion of subjects with hSBA titer ≥1:4 and ≥1:8 • hSBA geometric mean titer (GMT)

Objectives		Endpoints
		• hSBA titer distribution and reverse cumulative distribution curve (RCDC) • Proportion of subjects with hSBA titer ≥4-fold rise from baseline (Visit 1, D0, before vaccination) to after vaccination (Visit 2, D30 [+14 days])
	Safety	
	• To describe the safety profile of MenACYW conjugate vaccine and that of Menactra®	• Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, and relationship to vaccination, of any unsolicited systemic AEs reported in the 30 minutes after vaccination • Occurrence, time to onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and case report form [CRF]) injection site reactions occurring up to 7 days after vaccination • Occurrence, time to onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and CRF) systemic reactions occurring up to 7 days after vaccination • Occurrence, nature (MedDRA preferred term), time to onset, duration, intensity, action taken, relationship to vaccination (for systemic AEs only), and whether the event led to early termination from the study, of unsolicited AEs up to Visit 2 after vaccination • Occurrence, nature (MedDRA preferred term), time to onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the SAE led to early termination from the study, of SAEs throughout the study from Visit 1 (D0) to Visit 2 (D30 [+14 days]) after vaccination
Tertiary/exploratory	**Not Applicable**	

2 SAMPLE SIZE DETERMINATION

Approximately 360 healthy children, adolescents and adults (180 subjects per group) will be randomly assigned in a 1:1 ratio to the following vaccine groups:

- Group 1 (investigational): MenACYW conjugate vaccine (180 subjects)
- Group 2 (control): Menactra® (180 subjects)

[redacted]

Table 3 – Power of the study based on the primary objective of non-inferiority with [redacted] evaluable subjects per group

Serogroup	Estimated[a] MenACYW conjugate vaccine	Estimated[b] Menactra®	Non-inferiority margin	Power
[redacted]				

[redacted]

3 ANALYSIS POPULATIONS

The following populations for analyses are defined:

Table 4 - Populations for analyses

Population	Description
Enrolled	Enrolled subjects are subjects for whom a CRF has been created.
Randomized	A randomized subject is a subject for whom an injection group has been allocated.
Full Analysis Set (FAS)	The FAS is defined as the subset of randomized subjects who received at least one dose of the study vaccine and had a valid post-vaccination blood sample result. All subjects will be analyzed according to the vaccine group to which they were randomized.
Per-Protocol Analysis Set (PPAS)	The PPAS is a subset of the FAS. The subjects presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS: • Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria • Subject did not receive vaccine • Subject received a vaccine other than the one that he/she was randomized to receive • Preparation and/or administration of vaccine was not done as per-protocol • Subject did not receive vaccine in the proper time window • Subject did not provide post-dose serology sample in the proper time window or a post-dose serology sample was not drawn • Subject received a protocol-prohibited Category 2 or Category 3 therapy/medication/vaccine[ab] • Subject's serology sample did not produce a valid test result • Subject had other protocol violations that affected the subject's immune response, as determined by the clinical team before locking the database.
Safety Analysis Set (SafAS)	The SafAS is defined as those subjects who have received at least one dose of the study vaccine and have any safety data available. All subjects will have their safety analyzed according to the vaccine they actually received. Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).

a Protocol-prohibited therapy/medication/vaccine is defined as Restricted treatments during the study period in Section 6.7 Concomitant medication and other therapies of protocol.

b Category 3 should be considered as protocol-prohibited therapy if antibiotics are administered 3 days prior the blood sampling time point.

The immunogenicity analysis set consists of the FAS and the PPAS. The primary immunogenicity analyses will be performed on the PPAS, and will be confirmed on the FAS. In the FAS, subjects will be analyzed by the vaccine group to which they were randomized. The secondary and observational immunogenicity analyses will be also performed on both PPAS and FAS, unless otherwise specified.

All safety analyzed will be performed on the SafAS. Subjects will be analyzed according to the vaccine they actually received.

4 STATISTICAL ANALYSES

4.1 GENERAL CONSIDERATIONS

The statistical analyses will be performed under the responsibility of the Sponsor's Biostatistics platform using SAS® Version 9.4 software or later.

The result of the statistical analysis will be available in the final clinical study report (CSR).

In general, continuous data will be summarized using the number of observations available, mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum. Categorical and ordinal data will be summarized using the count and percentage of subjects.

Clinical safety results will be presented using number and percentage of subjects with corresponding 95% confidence interval (CI). Number of events will be also added for unsolicited events.

Regarding immunogenicity results, categorical data will be presented using number and percentage of subjects with their 95% CI. In order to provide geometric means (GMs) and their 95% CI, it is assumed that log_{10} transformation of the titers / data follows a normal distribution. At first, the mean and 95% CI will be calculated on log_{10} (titers / data) using the usual calculation formal distribution (using Student's t distribution with n-1 degree of freedom), then antilog transformations will be applied to the results of calculations.

The CI for the single proportion will be calculated using the exact binomial method (Clopper-Pearson method, quoted by Newcombe) (1). The CI for the difference in proportions will be calculated using the Wilson Score method without continuity correction, quoted by Newcombe (2). These calculations of the 95% CIs are detailed in Section 5.4.7.

4.2 PARTICIPANT DISPOSITIONS

Duration of the study will be presented using a summary table on Enrolled subjects.

The number (%) of enrolled subjects will be summarized by center and randomized vaccine group.

Vaccine allocation will be summarized by randomized vaccine group giving number (%) of subjects on enrolled subjects.

The number (%) of subjects in the following categories will be summarized on enrolled subjects:

- Enrolled subjects at Visit 1
- Randomized subjects at Visit 1
- Subjects who provided blood sample at Visit 1

- Subjects who received vaccine and received vaccine as randomized at Visit 1
- Subjects present at Visit 2
- Subjects who provided blood sample at Visit 2
- Subjects who completed the study
- Subjects who discontinued the study with following reasons of early termination
  - Adverse event
  - Protocol deviation
  - Lost to follow-up
  - Withdrawal by subject
  - Withdrawal by parent/guardian

The number (%) of randomized subjects will be summarized by following age category as randomization strata and vaccine group: 2 to 9 years (children), 10 to 17 years (adolescents), and 18 to 55 years (adults).

The number (%) of subjects included in immunogenicity analysis sets (FAS and PPAS) and SafAS listed in Table 4 will be summarized.

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be summarized in the randomized subjects.

4.3 PRIMARY ENDPOINT(S) ANALYSIS

4.3.1 Definition of endpoint(s)

The primary endpoint(s) for the evaluation of immunogenicity is vaccine seroresponse of meningococcal serogroups A, C, Y, and W measured by hSBA assessed at baseline (Visit 1, D0, before vaccination) and at Visit 2 (D30 [+14 days]) after vaccination for immune non-inferiority between MenACYW conjugate vaccine and Menactra® (Group 1 versus Group 2). The vaccine seroresponse for serogroups A, C, Y, and W is defined as post-vaccination hSBA titers ≥1:16 for subjects with pre-vaccination hSBA titers <1:8 or at least a 4-fold increase in hSBA titers from pre- to post-vaccination for subjects with pre-vaccination hSBA titers ≥1:8.

There are no primary objectives/endpoints for safety and efficacy.

4.3.2 Main analytical approach

The primary objective is non-inferiority of MenACYW conjugate vaccine compared to Menactra® in terms of hSBA vaccine seroresponse.

Thirty days after the administration of MenACYW conjugate vaccine or Menactra® vaccine, the percentage of subjects who achieve an hSBA vaccine seroresponse for meningococcal serogroups A, C, Y, and W in Group 1 are non-inferior to the corresponding percentages in Group 2.

Null hypothesis (H_0): $p_{(G1)} - p_{(G2)} \leq -10\%$
Alternative hypothesis (H_1): $p_{(G1)} - p_{(G2)} > -10\%$

where $p_{(G1)}$ and $p_{(G2)}$ are the percentages of subjects who achieve an hSBA vaccine seroresponse in Group 1 and Group 2, respectively. Each of the serogroups A, C, Y, and W will be tested separately. If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions is >-10%, the inferiority assumption will be rejected.

For the 4 non-inferiority hypotheses using the seroresponse rate, the CI of the difference in proportions will be computed using the Wilson Score method without continuity correction. The overall non-inferiority of this objective will be demonstrated if all 4 individual null hypotheses are rejected. The main statistical analyses will be performed on both the PPAS and FAS.

4.3.3 Sensitivity analysis

Not applicable

4.3.4 Supplementary analyses

Not applicable

4.3.5 Subgroup analyses

To assess the homogeneity of the treatment effect across various subgroups, analyses will be performed on the primary endpoint on the PPAS and FAS across the following subgroups:

- Age group (2 to 9 [children], 10 to 17 [adolescents], and ≥18 [adults])
- Sex (Male, Female)

No statistical testing will be performed for the subgroup analyses.

4.4 SECONDARY ENDPOINT(S) ANALYSIS

4.4.1 Key/Confirmatory secondary endpoint(s)

4.4.1.1 Definition of endpoint(s)

The secondary endpoint for immunogenicity is:

Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA assessed at baseline (D0, before vaccination) and after vaccination at D30 (+14 days) for all groups.

- hSBA vaccine seroresponse
- Proportion of subjects with hSBA titer ≥1:4 and ≥1:8
- hSBA GMT
- hSBA titer distribution and reverse cumulative distribution curve (RCDC)
- Proportion of subjects with hSBA titer ≥4-fold rise from baseline (Visit 1, D0, before vaccination) to after vaccination (Visit 2, D30 [+14 days])

4.4.1.2 Main analytical approach

Descriptive statistics will be provided on both the PPAS and FAS for the antibody titers against meningococcal serogroups contained in each lot of MenACYW conjugate vaccine and Menactra®.

RCDC figures will be provided on both the PPAS and FAS for the antibody titers against meningococcal serogroups.

In summary, descriptive analyses on A, C, Y, and W serogroups will be included in:

- hSBA vaccine seroresponse and 95% CI
- Post-vaccination hSBA GMT and 95% CI
- hSBA GMT and 95% CI at each time point
- hSBA titer distribution and RCDC
- Proportion of subjects with hSBA titer ≥1:4 and ≥1:8 and 95% CI at each time point
- Proportion of subjects with ≥4-fold rise of hSBA titer from pre-vaccination to post-vaccination

4.4.1.3 Subgroup analyses

Additional immunogenicity subgroup analyses by age group and sex will be performed on both the PPAS and FAS.

- hSBA vaccine seroresponse and 95% CI
- hSBA GMT and 95% CI at each time point

4.4.2 Supportive secondary endpoint(s)

Not applicable

4.5 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

4.5.1 Definition of endpoint(s)

Not applicable.

4.5.2 Main analytical approach

Not applicable.

4.6 MULTIPLICITY ISSUES

Overall non-inferiority of the primary objective will be declared only if all individual null hypotheses for the primary endpoint are rejected on the PPAS by main analytical approach of Section 4.3.2. Therefore, there is no issue with multiplicity.

4.7 SAFETY ANALYSES

All safety analyses will be performed on the SafAS as defined in Section 3, unless otherwise specified, using the following common rules:

- The analysis of the safety variables defined in Table 2 of Section 1.2 will be essentially descriptive, and no testing is planned. However, the 95% CI will be provided.
- Safety data in subjects who do not belong to the SafAS will be provided (in the listings of Appendix).

4.7.1 Extent of exposure

Not applicable

4.7.2 Adverse events

General common rules for adverse events

All adverse events (AEs) will be coded to a lower-level term (LLT), preferred term (PT), and associated primary system organ class (SOC) using the MedDRA version currently in effect at Sanofi at the time of database lock.

The AE tables will be sorted as indicated in Table 5.

Table 5 - Sorting of AE tables

AE presentation	Sorting rules
SOC and PT	By the primary SOC and PT alphabetical order

Safety overview

The safety overview after injection with the details below will be generated:

- Within 30 days after vaccine injection
  - Immediate unsolicited AE and adverse reaction (AR)
  - Solicited reaction
  - Solicited injection site reaction
  - Solicited systemic reaction
  - Unsolicited AE and AR
  - Unsolicited non-serious AE and AR
  - Unsolicited non-serious injection site AR
  - Unsolicited non-serious systemic AE and AR
  - AE leading to study discontinuation
  - Serious adverse event (SAE)
  - Death
- During the study
  - SAE
  - Death

The safety overview will also be generated by the following subgroups:

- (Actual) Age group (2 to 9 [children], 10 to 17 [adolescents], and ≥18 [adults])
- Sex (Male, Female)

Solicited reactions

The following summaries of solicited reactions within 7 days after vaccine injection will be presented using the terms prelisted in case report book (CRB):

- All and Grade 3 solicited reaction, solicited injection site reaction, and solicited systemic reaction
- Solicited reaction, each solicited injection site reaction (injection site pain, injection site erythema, injection site swelling, and injection site induration), and each solicited systemic reaction (fever, headache, malaise, and myalgia)
- Solicited injection site reactions (injection site pain, injection site erythema, injection site swelling, and injection site induration) and solicited systemic reactions (fever, headache, malaise, and myalgia) by following category:
  - By time period: D0-D3, D4-D7, D8 or later
  - By maximum intensity

- By time of onset
- By number of days of occurrence during the solicited period
- By action taken

Unsolicited AEs

The summary of unsolicited AEs within 30 days after vaccine injection with the details below will be generated:

- Immediate unsolicited AE and AR (any and Grade 3)
- Unsolicited AE and AR
- Unsolicited non-serious AE and AR (any and Grade 3)
- Unsolicited non-serious injection site AR (any and Grade 3)
- Unsolicited non-serious systemic AE and AR (any and Grade 3)
- SAE

The unsolicited non-serious AEs and ARs within 30 days after injection will also summarized by maximum intensity, time of onset and duration.

The AE summaries after vaccine injection of Table 6 will be generated with number (%) of participants experiencing at least one event. In the summaries, the 95% CI of proportion and number of AE/ARs will also be presented.

The all and related SAEs within 30 days after vaccine injection and during whole study will also be summarized by seriousness criterion and outcome.

Table 6 - Analyses of adverse events

Type of AE	MedDRA levels
All unsolicited AE within 30 days	Primary SOC and PT
All unsolicited AR within 30 days	Primary SOC and PT
Unsolicited non-serious AE within 30 days	Primary SOC and PT
Unsolicited non-serious AR within 30 days	Primary SOC and PT
Immediate unsolicited non-serious AE within 30 minutes after vaccine injection within 30 days	Primary SOC and PT
Grade 3 unsolicited non-serious AE within 30 days	Primary SOC and PT
Grade 3 unsolicited non-serious AR within 30 days	Primary SOC and PT
All and related AE leading to study discontinuation within 30 days	Primary SOC and PT
All and related AE leading to study discontinuation during the whole study	Primary SOC and PT
SAE	Overview[a]

Type of AE	MedDRA levels
	Primary SOC and PT

a Will include the following SAE category: all SAEs and related SAEs within 7 days after vaccine injection, within 30 days after vaccine injection, and during whole study

Analysis of deaths

The summary of death will be presented above in safety overview.

Analysis of adverse events of special interest (AESIs)

Not applicable.

4.7.3 Additional safety assessments

4.7.3.1 Laboratory variables, vital signs and electrocardiograms (ECGs)

Not applicable

4.8 OTHER ANALYSES

4.8.1 Assessment of impact of COVID-19 pandemic

In order to assess an impact of Coronavirus Disease 2019 (COVID-19) pandemic on study conduct, the number (%) of subjects in the following categories will be also summarized on enrolled subjects:

- Subjects with a CRF
- Subjects impacted by COVID-19 pandemic situation
- Subjects with at least one major/critical protocol deviation due to COVID-19 pandemic situation, and each detailed deviation
- Subjects who discontinued the trial with following reasons of early termination due to COVID-19
  - Adverse event
  - Protocol deviation
  - Lost to follow-up
  - Withdrawal by subjects
  - Withdrawal by parent/guardian
- Visit disposition at each visit
  - COVID-19 Visit not done

- COVID-19 Visit partially done: blood sampling not performed, vaccination not performed, and no solicited safety data available
- COVID-19 At least one procedure out of time window: blood sampling out of time window, vaccination out of time window, and visit date out of time window
- COVID-19 No procedure done on site
- COVID-19 At least one procedure done by phone
- COVID-19 At least one procedure done at home

4.9 INTERIM ANALYSES

No interim/preliminary analyses are planned.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

AE:	adverse event
AR:	adverse reaction
CI:	confidence interval
COVID-19:	Coronavirus Disease 2019
CRB:	case report book [all the case report forms for a subject]
CRF:	case report form
CSR:	clinical study report
D:	day
FAS:	Full Analysis Set
GM:	geometric mean
GMT:	geometric mean titer
hSBA:	serum bactericidal assay using human complement
IMP:	investigational medicinal product
LLOQ:	lower limit of quantitation
LLT:	lower-level term
MD:	missing data
MedDRA:	Medical Disctionary for Regulatory Activities
NM:	non-measurable, too large to measure
NSAID:	non-steroidal anti-inflammatory drug
PMDA:	Pharmaceuticals and Medical Device Agency
PPAS:	Per-Protocol Analysis Set
PT:	preferred term
Q1:	first quartile
Q3:	third quartile
RCDC:	reverse cumulative distribution curve
rSBA:	serum bactericidal assay using baby rabbit complement
SAE:	serious adverse event
SafAS:	Safety Analysis Set
SAP:	statistical analysis plan
SD:	standard deviation
SOC:	system organ class
ULOQ:	upper limit of quantitation
WHO-DD:	World Health Organization-drug dictionary

5.2 APPENDIX 2 CHANGES TO PROTOCOL-PLANNED ANALYSES

This section summarizes major statistical changes in the protocol amendment(s).

Table 7 - Major statistical changes in protocol amendment(s)

Amendment Number	Approval Date	Changes	Rationale
1	10-Mar-2020	No changes in protocol amendment	

5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

Demographics, medical history

The following demographics and baseline characteristics, and medical history will be summarized using descriptive statistics in the randomized subjects. The demographics and baseline characteristics will also be summarized in the FAS, PPAS, and SafAS.

Demographic and baseline characteristics

- age in years as quantitative variable and in categories (2 to 9 [children], 10 to 17 [adolescents], and ≥18 [adults])
- gender (Male, Female)
- race (White, Asian, Black, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Multiple, Not reported, and Unknown)
- ethnicity (Hispanic or Latino, Not Hispanic or Latino, Nor Reported, and Unknown)

Medical history includes conditions/illnesses for which the subject is or has been followed by a physician or condition/illnesses that could resume during the course of the study or lead to an SAE or to a repetitive outpatient care will be collected in the CRB. Medical history will not be codded using the MedDRA.

Concomitant medications

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

Documentation in the CRB of ongoing concomitant medication(s) will be limited to specific categories of medication(s) of interest beginning on the day of vaccination. This may include medications of interest that were started prior to the day of vaccination.

Reportable medications will be collected in the CRB from the data of vaccination to the end of the study (D30 [+14 days]).

Reportable medications include medications that impact or may impact the consistency of the safety information collected after vaccination and/or the response to vaccination. Three standard categories of reportable medications are defined:

- Category 1: antipyretics, analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and other immune modulators.
  - Note: inhaled and topical steroids should not be captured.
- Category 2: Reportable medications used to define the Per-Protocol Analysis Set (PPAS). For example:
  - Influenza and other non-study vaccines: Influenza vaccine in the 2 weeks preceding the study vaccination up to the subject's termination from the study and any other vaccines (other than the study vaccine) in the 4 weeks preceding the study vaccination up to the subject's termination from the study
  - Immune globulins, blood or blood-derived products: used in the 3 months preceding the first blood draw and up to the last blood draw
  - Immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy: used in the 6 months preceding the study vaccination and the 4 weeks following the study vaccination
- Category 3: Oral or injectable antibiotics, which may interfere with bioassays used for antibody testing when taken before a blood draw.

Protocol-prohibited therapy, medication or vaccines

In general, the "prohibited" variable is not derived. All concomitant medications are reviewed by the clinical team and the value of "prohibited" variable is determined before database lock by the clinical team according to the following rule:

Only two categories of reportable medications will be considered as prohibited therapy, medication or vaccine

Category 2:

- Flu vaccines administered within 14 days pre or post each trial vaccination, including the day of the study visit vaccination
- Other vaccines not included as study vaccines, it means non-study vaccines (e.g. Oral poliovirus, Yellow fever, Japanese encephalitis, or other routine/not-routine vaccine not-described in the protocol) within the 28 days (4 weeks) preceding or after the trial vaccination, including the day of the study visit vaccination
- Immune globulins, blood or blood-derived products and Immunosuppressive therapy, as described in the protocol

Category 3:

- Antibiotics that the subject received within the 3 days preceding each Visit for blood draw related to investigational medicinal product (IMP) assessment (meningococcal vaccines)

If the above protocol-prohibited therapy, medication or vaccines are received at specific visits, it will impact the corresponding immunogenicity analyses.

The reportable medications will be summarized for the enrolled subjects. The summary will be presented based on the use of any medication and each category, and the medication considered by the sponsor as the protocol-prohibited treatment will also be summarized.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

5.4.1 General conventions

Subject duration

The duration of a subject in the study is computed as follows:

Maximum (date of last visit, date of termination form) – (date of Visit 1) + 1.

Duration of the Study

The duration of the study (until last visit) is computed as follows:

Maximum of all subjects (date of last visit, date of termination form)
– minimum for all subjects (date Visit 1) + 1.

5.4.2 Data handling conventions for safety variables

5.4.2.1 Solicited Reactions

Daily intensity

All daily records for solicited reactions will be derived into daily intensity according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing. The category of Unknown will be considered Missing if Unknown is recorded.

For the derivation of daily intensities, the following sequential steps will be applied:

1. Solicited reactions (except Fever/Pyrexia) with an investigator presence recorded as “No” and with all daily records missing then all daily intensities will be derived as None.
2. For a temperature partially missing after decimal point, the data will be analyzed replacing “MD” (missing data) by zero. For example, a “39.MD” daily temperature will be considered as “39.0°C” at the time of analysis.
3. For non-measurable (NM) solicited reactions, daily intensities will correspond to daily records reported in the clinical database. For measurable solicited reactions the daily measurements reported in the clinical database will be converted based upon the intensity scales defined in the protocol; this assumes a reaction that is too large to measure (NM) is Grade 3. Note the intensity could be considered “None” (not reaction) in the analysis despite being considered a reaction by the investigator (e.g., swelling measurement > 0 mm but < 25 mm in adults).

Note: The maximum intensity on the ongoing period is derived from the record of the maximum intensity/measurement after the end of the solicited period following the rule described above in "Daily intensity".

Maximum overall intensity

Maximum overall intensity is derived from the daily intensities computed as described above in "Daily intensity" and is calculated as the maximum of the daily intensities over the period considered.

Presence

Presence is derived from the maximum overall intensity on the period considered:

- None : No presence
- Grade 1, Grade 2, or Grade 3 : Presence
- Missing : Missing presence

Subjects with at least one non-missing presence for a specific endpoint will be included in the analysis. Conversely, those without a non-missing presence will not be included in the analysis of the endpoint.

Time of onset

Time of onset is derived from the daily intensities computed as described above in "Daily intensity". It corresponds to the first day with intensity of Grade 1, Grade 2, or Grade 3.

Note: If a reaction is not continuous (i.e., reaction occurs over two separate periods of time intervened by at least one daily intensity Missing or None) then the time of onset is the first day of the first occurrence.

Number of days of occurrence

Number of days of occurrence over the period considered is derived from the daily intensities computed as described above in "Daily intensity". It corresponds to the number of days with daily intensities of Grade 1, Grade 2, or Grade 3. Number of days of occurrence on the solicited period with a specified intensity may also be derived.

Overall number of days of occurrence

If a reaction is ongoing at the end of the solicited period, then the overall number of days of occurrence is derived from the daily intensities and the stop date of the reaction after the end of the solicited period. The overall number of days of occurrence is:

(stop date – last vaccination date)

+ (number of days of occurrence within the solicited period)

– length of the solicited period + 1

If the stop date is missing or incomplete (contains MD), the overall number of days of occurrence will be considered as Missing.

Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described above in "Daily intensity" and the maximum intensity on the ongoing period. The investigator's ongoing flag is not used because the measurement would determine the ongoing status of the reaction.

If the last daily intensity of the solicited period is at least Grade 1 and maximum intensity on the ongoing period is also at least Grade 1, then the reaction is considered ongoing. In any other cases the reaction will not be considered as ongoing.

5.4.2.2 Unsolicited Non-serious AEs

Presence

An observation will be considered an event if it has at least a verbatim term and is not a Grade 0 intensity event. Grade 0 events should be included in the listing "Unsolicited non-serious adverse events not included in the safety analysis."

Intensity

Intensity for unsolicited non-serious AE will be derived according to the following classification: None: Grade 1, Grade 2, Grade 3, or Missing. The category of Unknown will be considered Missing if Unknown is recorded as well as the intensity classification of solicited reactions.

If the unsolicited non-serious AE is measurable and its preferred term is part of the list of solicited reactions, then the measurement is derived based upon and following the same rule than the intensity scales defined in the protocol for that measurable injection site or systemic reaction.

Intensity for the other unsolicited non-serious AEs will correspond to the value reported in the CRF.

The maximum intensity corresponds to the highest intensity for a unique term.

Last vaccination

Last vaccination before any unsolicited non-serious AE is the study vaccination at Visit 1.

Time of onset

Time of onset is derived from the start date of the unsolicited non-serious AE provided in the clinical database and the date of last vaccination:

start date of the unsolicited non-serious AEs – date of previous vaccination

The time of onset should be considered as missing only if one or both of the dates are missing or partially missing.

The unsolicited non-serious AEs will be analyzed "Within 30 days", which corresponds to AEs with a time of onset between 0 and 30 days after vaccination or missing. An AE with missing time of onset will be considered to have occurred just after the vaccination indicated by the visit number, so will be included in these tables.

Note: Unsolicited non-serious AEs that occurred before vaccination (negative time of onset) or with a time of onset higher than defined above will not be included in analysis, but will be listed separately.

Duration

Duration is derived from the start and stop dates of the unsolicited non-serious AE provided in the clinical database:

stop date of unsolicited non-serious AE – start date of unsolicited non-serious AE + 1.

The duration should be considered as missing only if one or both of the start and stop dates of the unsolicited non-serious AE is missing or partially missing.

5.4.2.3 SAEs

Last vaccination

The last vaccination before any SAE is defined as the study vaccination at Visit 1.

Time of onset

Time of onset will be computed using the same methodology than for unsolicited non-serious AEs described in Section 5.4.2.2.

SAEs will be analyzed throughout the study using the following periods:

- During the study (i.e., all SAEs occurred during the study)
- Within 30 days after vaccination

An SAE with missing time of onset will be considered to have occurred just after the vaccination indicated by the visit number, so will be included in these tables.

Note: SAEs that occurred before vaccination (negative time of onset) will not be included in analysis, but will be listed separately.

Duration

Duration will be computed using the same methodology than for unsolicited non-serious AEs described in Section 5.4.2.2.

5.4.2.4 Other Safety Endpoints

Pregnancy

This information will be listed as collected. No derivation or imputation will be done.

Action taken

This information will be summarized as collected, including missing observation. No derivation or imputation will be done.

Seriousness

This information will be summarized as collected. No derivation or imputation will be done.

Outcome

This information will be summarized as collected. No derivation or imputation will be done.

Causality

This information will be summarized as collected. Missing causality (relationship) will be handled as described in Section 5.4.4.1.

AEs leading to study discontinuation

A flag is available in the clinical database for all AEs in order to identify AEs leading to discontinuation.

In general, the items that are counted are:

- Disposition table: A subject who has, on the termination form, the reason for early termination “Adverse Event” is checked.
- Safety overview table: A subject who has either on the termination form the reason for early termination “Adverse Event” is checked or lists an AE on an AE page (solicited, unsolicited) that has “Caused Study Termination” checked that is at least Grade 1 and is within the time period indicated.
- System Organ Class/Preferred Term (SOC/PT) table: An event (solicited, unsolicited, or SAE) that has “Caused Study Termination” checked that is at least Grade 1 and is within the time period indicated.

5.4.3 Data handling conventions for immunogenicity variables

Computed values for analysis

In order to appropriately manage extreme values (undetectable responses <lower limit of quantitation [LLOQ] and ≥upper limit of quantitation [ULOQ]), the following computational rule is applied to the values provided in the clinical database for each blood sample drawn for analysis purpose:

- If a value is <LLOQ, then use the computed value LLOQ/2
- If a value is between ≥LLOQ and <ULOQ, then use the value
- If a value is ≥ULOQ, then use the computed value ULOQ

Fold-rise

The derived endpoint of fold-rise is computed as follows for extreme values, to minimize the numerator and maximizes the denominator:

- If the baseline computed value is <LLOQ and the post-baseline computed value is <LLOQ then the fold-rise is 1 fold for the baseline
- If the baseline computed value is ≥LLOQ and the post-baseline computed value is ≥LLOQ then the fold-rise is post-baseline computed value / baseline computed value
- If the baseline computed value is ≥LLOQ and the post-baseline computed value is <LLOQ then the fold-rise is (LLOQ/2) / baseline computed value
- If the baseline computed value is <LLOQ and the post-baseline computed value is ≥LLOQ then the fold-rise is post-baseline computed value / LLOQ

Vaccine seroresponse

hSBA vaccine seroresponse for serogroups A, C, Y, and W is defined as:

- For a subject with a pre-vaccination titer <1:8, then post-vaccination titer must be ≥1:16.
- For a subject with a pre-vaccination titer ≥1:8, then post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer.

5.4.4 Missing data

5.4.4.1 Safety

No replacement will be done. In all subject listings, partial and missing data will be clearly indicated as missing.

Immediate

For unsolicited non-serious systemic AEs, a missing response to the "Immediate" field is assumed to have occurred after the 30-minute surveillance period and will not be imputed.

For SAEs, missing or partially missing elapsed time from last vaccination recorded if within 24 hours will be assumed to have occurred after the 30-minute surveillance period and will not be imputed. Such SAEs will not be considered as immediate.

Causality

Missing causality (relationship) for unsolicited non-serious AEs and SAEs will be considered at the time of analysis as related to vaccination.

Measurements

Partially missing temperatures will be handled as described in "Daily intensity" of Section 5.4.2.1.

Intensity

For solicited reactions, missing intensities will be handled as described in "Daily intensity" of Section 5.4.2.1. For unsolicited non-serious AEs, missing intensities will remain missing and will not be imputed.

Start Date and Stop Date

Missing or partially missing start dates for unsolicited AEs will remain missing and not be imputed. If the start date is missing or partially missing, the time of onset will be considered to be missing. Nevertheless, unsolicited AEs with missing time of onset will be included in analyses according to the visit collected.

Missing or partially missing stop dates for AEs (solicited reactions and unsolicited AEs) will remain missing and not be imputed.

5.4.4.2 Immunogenicity

Missing data will not be imputed. No test or search for outliers will be performed.

5.4.5 Windows for time points

Analysis windows for time points

A measurement at each visit will be used for immunogenicity according to following table defined in the protocol. Solicited reactions and unsolicited (non-serious/serious) AEs observed at time of onset mentioned in Section 5.4.2 will be analyzed for safety analyzes.

Table 8 – Study procedure window definition

Visit / Contact	Visit 1	Telephone Call 1	Visit 2
Study timelines (days)	Day 0	Day 8	Day 30
Time windows (days)	-	+2 days	+14 days

5.4.6 Pooling of centers for statistical analyses

All data from each center will be pooled and analyzed as Enrolled subjects, Randomized subjects, FAS, PPAS, and SafAS.

5.4.7 Statistical technical issues

Confidence interval for the individual group GMT

The 2-sided 95% CI for the individual group GMT will be computed using the normal approximation as

$$10^{\left(\bar{x} \pm t_{n-1,\alpha/2}\sqrt{v(\bar{x})}\right)}$$

where $10^{(\bar{x})}$ is the GMT, $\bar{x} = \sum \log_{10}(x)/N$ and $\log_{10}(x)$ is the log base 10 of the observed titer, N is the total observation is each vaccination group, $\sqrt{v(\bar{x})}$ is the estimated standard deviation of $\bar{x}$, $\alpha = 0.05$ and $t_{n-1,\alpha/2}$ is the $100(1-\alpha/2)$ percentile of the central *t*-distribution with *n*-1 degrees of freedom.

Confidence interval for the GMT ratio between 2 groups

For each of the GMT ratios, the statistical methodology will be based on the use of the 2-sided 95% CI of difference in means of post-vaccination $\log_{10}$ transformed titers between the 2 groups with normal approximation.

The 95% CI for the difference in $\log_{10}$ (GMT) between Group 1 and Group 2 will be in the form:

$$\bar{X}_1 - \bar{X}_2 \pm t(1-\alpha/2, n_1+n_2-2) \cdot S\sqrt{\frac{1}{n_1}+\frac{1}{n_2}},$$

where $\bar{X}_i$ =$\log_{10}$(GMT) is the mean of $\log_{10}$(titer) of Group *i*,

$S^2 = [(n_1 - 1)S_1^2 + (n_2 - 1)S_2^2]/(n_1 + n_2 - 2)$ is the pooled sample variance,

n_i and S_i^2 are the sample size and sample variance of Group *i*,

$t(1 - \alpha/2, n_1 + n_2 - 2)$ is the $100(1 - \alpha/2)$percentile of the *t*-distribution with degrees of freedom $df = n_1 + n_2 - 2$.

The 95% CI for the ratio of GMTs can be obtained by taking antilog transformations for the calculated 95% CI for the difference in $\log_{10}$(GMT).

Confidence interval for the single proportions

The 95% CI for the single proportions will be constructed using the exact binomial method (Clopper-Pearson's method, i.e., using the inverse of the beta integral with SAS®):

Lower bound: $1 - Beta(0.975, n - r + 1, r)$

Upper bound: $Beta(0.975, r + 1, n - r)$,

Where r is the observed number of events/responders in n observations.

Confidence interval of the difference in proportions

The 2-sided CI of the difference in proportions will be computed using the Wilson Score method without continuity correction, quoted by Newcombe (2).

Let $\hat{\theta} = p_1 - p_2$, then $L = \hat{\theta} - \delta$ and $U = \hat{\theta} + \varepsilon$ are respectively the lower and the upper limits of the CI, where:

$$\delta = Z_{0.025}\sqrt{\left\{\frac{l_1(1-l_1)}{n_1} + \frac{u_2(1-u_2)}{n_2}\right\}}$$

$$\varepsilon = Z_{0.025}\sqrt{\left\{\frac{l_2(1-l_2)}{n_2} + \frac{u_1(1-u_1)}{n_1}\right\}},$$

l_1 and u_1 are calculated from the CI of the pooled proportion in Group 1 given by:

$$\frac{\left(2n_1p_1 + Z^2_{0.025} \pm Z_{0.025}\sqrt{\left(Z^2_{0.025} + 4n_1p_1(1-p_1)\right)}\right)}{2(n_1 + Z^2_{0.025})},$$

l_2 and u_2 are calculated from the CI of the single proportion in Group 2 given by:

$$\frac{\left(2n_2p_2 + Z^2_{0.025} \pm Z_{0.025}\sqrt{\left(Z^2_{0.025} + 4n_2p_2(1-p_2)\right)}\right)}{2(n_2 + Z^2_{0.025})},$$

where $Z_{0.025}$ is the upper 97.5th percentile of the standard normal distribution, and n_i is the total sample size and p_i = (total # of seroresponders in Group *i*) / n_i of Group *i* (*i*=1,2).

6 REFERENCES

1. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med. 1998; 17(8):857-72.

2. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med. 1998; 17(8):873-90.

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