STATISTICAL ANALYSIS PLAN	
Detailed Title:	A Phase IIIB, Observer-Blind, Randomized, Placebo-Controlled, Multi-Center Study to Assess the Safety and Immunogenicity of GSK Meningococcal Group B Vaccine and 13-valent Pneumococcal Vaccine when Administered Concomitantly with Routine Vaccines to Healthy Infants
e-Track study number and Abbreviated Title	205239 (MENB REC 2ND GEN-023 (V72_57)).
Scope:	All data pertaining to the above study.
Date of Statistical Analysis Plan	Amendment 5 Final: 26 Jun 2025
Co-ordinating author:	PPD (Study Lead Statistician)
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APP 9000058193 Statistical Analysis Plan Template (Effective date: 14 April 2017)

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LIST OF ABBREVIATIONS

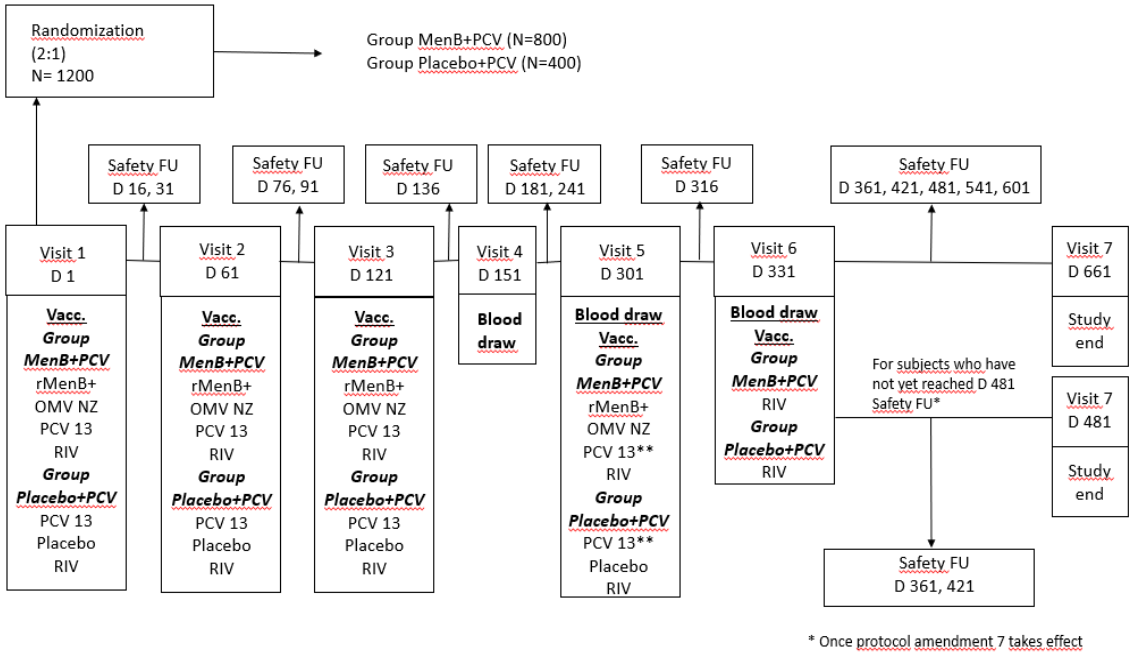
AE	Adverse event
AESI	Adverse Events of Special Interest
ANOVA	Analysis of Variance
CI	Confidence Interval
CRF	Case Report Form
CTRS	Clinical Trial Registry Summary
ECL	Electrochemiluminescence
ELISA	Enzyme-linked immunosorbent assay
ES	Exposed Set
FAS	Full Analysis Set
GMC	Geometric mean antibody concentration
GMR	Geometric Mean Ratio
GMT	Geometric mean antibody titer
GSK	GlaxoSmithKline
IU/ml	International units per milliliter
LLOQ	Lower Limit of Quantitation
LOD	Lower Limit of Detection
MedDRA	Medical Dictionary for Regulatory Activities
OPS	Output and Programming Specification
pIMD	Potential Immune-Mediated Disease
PPS	Per Protocol Set
RIV	Routine Infant Vaccines
SAE	Serious adverse event
SR	Study Report
TFL	Tables Figures and Listings
TOC	Table of Content

1. DOCUMENT HISTORY

Date	Description	Protocol Version
05 February 2018	Final	Protocol Amendment 2 (11 December 2017)
05 November 2018	Amendment 1	Protocol Amendment 4 (02 November 2018)
24 May 2022	Amendment 2	Protocol Amendment 6 (09 December 2021)
7 July 2023	Amendment 3	Protocol Amendment 7 (24 October 2022)
26 Jun 2025	Amendment 4	Protocol Amendment 8 (19 December 2023)
26 Jun 2025	Amendment 5	Protocol Amendment 8 (19 December 2023)

2. STUDY DESIGN

Figure 1 Overview of Study Design - V72_57



D: day; Vacc: vaccination, FU: follow-up call, RIV: routine infant vaccines (Visit 1 and Visit 2: DTPa-HBV-IPV, HRV, Hib; Visit 3: DTPa-HBV-IPV, Hib; Visit 5: MMR, VV).

- **Experimental design**: Phase IIIB, observer-blind, randomized, placebo-controlled, multi-centric study with 2 parallel groups.
- **Duration of the study:**
  - Epoch 001: Primary starting at Visit 1 (Day 1) and ending at Visit 5 (Day 301).
  - Epoch 002: Secondary starting at Visit 5 (Day 301) and ending at Visit 6 (Day 331).
  - Epoch 003: Safety follow-up period starting at Visit 6 (Day 331) and ending at Visit 7 (Day 481 or Day 661). For subjects who have not yet reached the 6-

month safety follow-up after the last dose at the time protocol amendment 7 took effect, Visit 7 will take place on Day 481**.**

- **Primary completion Date (PCD)**: Visit 7 (Day 481 or Day 661).

Refer to Protocol Glossary of terms for the definition of PCD.

- **End of Study (EoS)**: Date of the last testing/reading released of the Human Biological Samples (HBS) related to primary and secondary endpoints. Study completion must be achieved no later than 8 months after LSLV.

Refer to Protocol Glossary of terms for the definition of EoS.

- **Study groups**:
  - Group MenB+PCV: rMenB+OMV NZ vaccine given concomitantly with PCV13 at 2, 4, 6 and 12 months of age. Either PCV13 or PCV20 is allowed to be given at 12 months of age (Visit 5)for subjects who have not reached Visit 5 at the time protocol amendment 8 becomes effective. Subjects should also receive routine infant vaccines (DTaP-HBV-IPV**,** HRV, Hib, MMR, VV) at applicable timepoints.
  - Group Placebo+PCV: PCV13 vaccine given concomitantly with Placebo at 2, 4, 6 and 12 months of age. Either PCV13 or PCV20 is allowed to be given at 12 months of age (Visit 5) for subjects who have not reached Visit 5 at the time protocol amendment 8 becomes effective. Subjects should also receive routine infant vaccines (DTaP-HBV-IPV**,** HRV, Hib, MMR, VV) at applicable timepoints.

Table 1 Study Groups and Epochs Foreseen in the Study

Study Groups	Number of subjects	Age (Min – Max)	Epochs		
			Epoch 001	Epoch 002	Epoch 003
MenB+PCV	800	6 weeks – 12 weeks	x	x	x
Placebo+PCV	400	6 weeks – 12 weeks	x	x	x

Table 2 Study Groups and Treatment Foreseen in the Study

Treatment name	Vaccine name	Study Groups	
		MenB+PCV	Placebo+PCV
Bexsero	rMenB+OMV NZ	X	-
Prevnar13	PCV13*	X	X
Prevnar20	PCV20*	***X***	***X***
Placebo	NaCl	-	X
Pediarix	DTPa-HBV-IPV	X	X
Rotarix	HRV	X	X
Hiberix	Hib	X	X
M-M-R II	MMR	X	X
Varivax	VV	X	X

Note: Subjects in both groups will receive a fourth dose of Hib vaccine (*Hiberix*) and a single dose of DTPa vaccine (*Infanrix*) as non-study vaccines at Visit 6.
* Either PCV13 or PCV20 is allowed to be given at 12 months of age (Visit 5) for subjects who have not reached Visit 5 at the time protocol amendment 8 becomes effective.

Table 3 Overview of the Study Design: Blood Draws and Study vaccines

Clinic Visits (Study Day)		Visit 1 (Day 1)	Visit 2 (Day 61)	Visit 3 (Day 121)	Visit 4 (Day 151)	Visit 5 (Day 301)	Visit 6 (Day 331)
Months of Age (MoA)		~2 MoA[1]	4 MoA	6 MoA	7 MoA	12 MoA	13 MoA[3]
Study Vaccines	Group MenB+PCV N=800	rMenB+ OMV NZ PCV13	rMenB+ OMV NZ PCV13	rMenB+ OMV NZ PCV13	*Blood Draw*[2]	*Blood Draw*[2] rMenB+ OMV NZ PCV13[4]	*Blood Draw*[2, 3]
	Group Placebo+PCV N=400	Placebo PCV13	Placebo PCV13	Placebo PCV13		*Blood Draw*[2] Placebo PCV13[4]	
Routine Study Vaccines	**Both groups** N=1200	DTPa-HBV-IPV HRV Hib	DTPa-HBV-IPV HRV Hib	DTPa-HBV-IPV Hib		MMR VV	

MOA, months of age.
[1] Age at enrolment can be between 6 weeks to 12 weeks of age.
[2] Blood draw to be performed prior to any vaccination (study or non-study).
[3] Subjects in both groups will receive a fourth dose of Hib vaccine (*Hiberix*) and a single dose of DTPa vaccine (*Infanrix*) at 13 months of age, i.e. Visit 6 at Day 331. No immunogenicity or safety assessments will be performed following these Visit 6 vaccinations.
[4] Either PCV13 or PCV20 is allowed to be given at 12 months of age (Visit 5) for subjects who have not reached Visit 5 at the time protocol amendment 8 becomes effective.

Note: Study visits do not include safety follow-up calls. Although not conducted face-to-face, safety calls are intended for safety data collection. For details, refer to Table 5

- **Control**: placebo control.
- **Vaccination schedule**: Visit 1 (Day 1), Visit 2 (Day 61) Visit 3 (Day 121), Visit 5 (Day 301).
- **Treatment allocation**: Subjects to be randomized in a 2:1 ratio at Visit 1 (Day 1) to Groups MenB+PCV and Group Placebo+PCV, respectively.

Refer to Protocol amendment 8 (19DEC2023) Section 5.2 for a detailed description of the randomization method.

- **Blinding**: observer-blind study.

Table 4 Blinding of Study Epochs

Study Epochs	Blinding
Epoch 001	Observer-blind
Epoch 002	Observer-blind
Epoch 003	Observer-blind

- **Sampling schedule**: The sampling schedule for both study groups is the same. Three blood samples of approximately 5 ml each are to be taken at:
  - Visit 4 (Day 151), i.e., 30 (-9 to +30) days after the 3rd vaccination.
  - Visit 5 (Day 301), i.e., 180 (-7 to +91) days after the 3rd vaccination (pre-4th vaccination).
  - Visit 6 (Day 331), i.e., 30 (-9 to +30) days after the 4th vaccination.
- **Type of study**: self-contained.
- **Data collection**: Standardized Electronic Case Report Form (eCRF). Solicited symptoms will be collected using a subject Diary (electronic Diary [e-Diary]).

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary Safety	
• To assess the safety and tolerability of rMenB+OMV NZ, PCV13 and other RIV when administered concomitantly to healthy infants at 2, 4, 6 and 12 months of age, throughout the study duration.	• The percentages of subjects with solicited local Adverse events (AEs) (administration site events) and systemic AEs during the 7 days (including the day of vaccination) after the 1st, the 2nd, the 3rd and the 4th vaccination (Visits 1, 2, 3 and 5). • The percentages of subjects with solicited systemic AEs of parotid/salivary gland swelling, fever and rash during the 30 days (including the day of vaccination) after the 4th vaccination (Visit 5). • The percentages of subjects with all unsolicited AEs (including SAEs, AEs leading to withdrawal, AESIs, and medically attended AEs) during 30 days (including the day of vaccination) after the 1st, the 2nd, the 3rd and the 4th vaccination (Visits 1, 2, 3 and 5). • The percentages of subjects with SAEs, AEs leading to withdrawal, AESIs and medically attended AEs from study Day 1 (Visit 1) until study end (6 months or 12 months after last study vaccination, Visit 7¥).
Co-Primary Immunogenicity	
• To demonstrate the sufficiency of the immune response to rMenB+OMV NZ when administered concomitantly with PCV13 and other RIV to healthy infants at 2, 4 and 6 months of age, at one month after the 3rd vaccination. Criteria: The sufficiency of the immune response to rMenB+OMV NZ at one month after the 3rd vaccination will be demonstrated if the adjusted lower confidence limit for the percentage of subjects achieving serum bactericidal assay using human complement (hSBA) titers ≥ Lower Limit of Quantitation (LLOQ) is ≥ 60% for the N. meningitidis serogroup B test strains M14459, 96217, NZ98/254, M13520 (individually); and is ≥ 50% for all strains combined (composite endpoint).	• At 1 month after the 3rd vaccination (Day 151): – the percentages of subjects with hSBA titers ≥LLOQ; for each of the M14459, 96217, NZ98/254 and M13520 test strains. – the percentages of subjects with hSBA titers ≥LLOQ for all strains combined (composite endpoint).

Objectives	Endpoints
• To demonstrate the sufficiency of the immune response to rMenB+OMV NZ when administered concomitantly with PCV13 and other RIV to healthy infants at 2, 4, 6 and 12 months of age, at one month after the 4th vaccination. Criteria: The sufficiency of the immune response to rMenB+OMV NZ will be demonstrated if the adjusted lower confidence limit for the percentage of subjects with hSBA titers ≥ 8 (for strains M14459, NZ98/254, M13520) and ≥16 (for strain 96217) is ≥75% for the individual N. meningitidis serogroup B test strains and is ≥65% for all strains combined (composite endpoint).	• At 1 month after the 4th vaccination (Day 331): – the percentages of subjects with hSBA titers ≥ 8 (for strains M14459, NZ98/254, M13520) and ≥16 (for strain 96217) for each of the test strains. – the percentages of subjects with hSBA titers ≥ 8 (for strains M14459, NZ98/254, M13520) and ≥16 (for strain 96217) for all strains combined (composite endpoint).
• To demonstrate the immunological non-inferiority of PCV13 when administered concomitantly with rMenB+OMV NZ and other RIV to healthy infants 2, 4 and 6 months of age, compared to PCV13 without rMenB+OMV NZ, at one month after the 3rd vaccination. Criterion: The immunological non-inferiority of PCV13 will be demonstrated if the adjusted lower confidence limit for the between-group ratio of electrochemiluminescence (ECL) assay GMCs is >0.5 for each of the 13 PCV13 antigens.	• At 1 month after the 3rd vaccination (Day 151): – the ECL GMCs for each of the 13 PCV13 antigens.
Secondary Immunogenicity	
• To demonstrate the immunological non-inferiority of PCV13 when administered concomitantly with rMenB+OMV NZ and other RIV to healthy infants 2, 4, 6 and 12 months of age, compared to PCV13 and other RIV alone, at one month after the 4th vaccination. Criterion: The immunological non-inferiority of PCV13 will be demonstrated if the lower limit of 2-sided 95% CI for the between-group-ratio of ECL assay GMCs is >0.5 for each of the 13 PCV13 antigens.	• At one month after the 4th vaccination (Day 331): – The ECL GMCs for each of the 13 PCV13 antigens.
• To demonstrate the immunological non-inferiority of PCV13 when administered concomitantly with rMenB+OMV NZ and other RIV to healthy infants at 2, 4, 6 and 12 months of age compared to PCV13 and other RIV alone, at both one month after the 3rd and the 4th vaccinations. Criterion: The immunological non-inferiority of PCV13 will be demonstrated if the lower limit of the 2-sided 95% CI for the group differences in percentage of subjects with IgG ≥ 0.35 µg/mL is >-10% for each of the 13 PCV13 antigens at one month after both 3rd and 4th vaccination.	• At 1 month after the 3rd (Day 151) and the 4th vaccination (Day 331): – Percentages of subjects with serum pneumococcal anti-capsular polysaccharide IgG ≥0.35 µg/mL for each of the 13 PCV13 antigens.
• To demonstrate the immunological non-inferiority of DTaP-HBV-IPV and Hib vaccines when administered concomitantly with rMenB+OMV NZ and PCV13 to healthy infants at 2, 4, and 6 months compared to DTaP-HBV-IPV and Hib vaccines concomitantly administered with PCV13 without rMenB+OMV NZ, in terms of D, T, PT,	• At 1 month after the 3rd vaccination (Day 151): – GMCs against the 3 pertussis antigens (Pertussis toxin [PT], pertactin [PRN], filamentous hemagglutinin [FHA]). – Percentages of subjects with anti-HBs antibody concentrations ≥10 mIU/mL.

Objectives	Endpoints
FHA, PRN, Hep B and Hib, at one month after the 3rd vaccination. Criterion: The immunological non-inferiority will be demonstrated if the lower limit of the 2-sided 95% CI for the between-group differences is greater than the pre-specified margin† for each antigen at one month after 3rd vaccination.	– Percentages of subjects with anti-diphtheria and anti-tetanus concentrations ≥0.1 IU/mL. – Percentages of subjects with anti-PRP concentration ≥0.15 µg/mL and ≥1 µg/mL.
• To demonstrate the immunological non-inferiority of MMR and VV vaccines when administered concomitantly with rMenB+OMV NZ and PCV13 to healthy subjects at 12 months compared to MMR and VV vaccines concomitantly administered with PCV13, without rMenB+OMV NZ, at one month after vaccination. Criterion: The immunological non-inferiority will be demonstrated if the lower limit of the 2-sided 95% CI for the between-group ratio of GMCs is >0.67 at one month after the MMR and VV vaccinations.	• At 1 month after the 4th vaccination (Day 331): – GMCs against measles, mumps, rubella and VZV antigens.
• To evaluate the immune response to rMenB+OMV NZ when administered concomitantly with PCV13 and other RIV to healthy infants at 2, 4, 6 and 12 months of age, at one month after the 3rd vaccination, at 6 months after the 3rd vaccination (immediately before the 4th vaccination), and at one month after the 4th vaccination against the M14459, 96217, NZ98/254 and M13520 test strains.	• At 1 month after the 3rd vaccination (Day 151) – the percentages of subjects with hSBA titers ≥5, ≥8 and ≥16 for each of the M14459, 96217, NZ98/254 and M13520 test strains. – the hSBA geometric mean titers (GMTs) against each strain. • At 6 months after the 3rd vaccination (Day 301, immediately before the 4th vaccination): – the percentages of subjects with hSBA titers ≥LLOQ for each of the M14459, 96217, NZ98/254 and M13520 test strains. – the percentages of subjects with hSBA titers ≥5 and ≥8 for each of the M14459, 96217, NZ98/254 and M13520 test strains. – the hSBA GMTs against each strain. • At 1 month after the 4th vaccination (Day 331): – the percentages of subjects with hSBA titers ≥LLOQ for each of the M14459, 96217, NZ98/254 and M13520 test strains. – the percentages of subjects with hSBA titers ≥5 for each of the M14459, 96217, NZ98/254 and M13520 test strains. – the hSBA GMTs and geometric mean ratios (GMRs) over pre-4th vaccination against each strain. – the percentages of subjects with 4-fold rise* in hSBA titers (from pre-4th vaccination) for each of the M14459, 96217, NZ98/254 and M13520 test strains.

Objectives	Endpoints
• To evaluate immune responses to routine infant vaccines DTaP-HBV-IPV, Hib, MMR and VV vaccines when administered concomitantly with rMenB+OMV NZ and PCV13 to healthy infants at 2, 4, 6 and 12 months of age, at one month after the 3rd vaccination, at 1 month after the 4th vaccination.	• At 1 month after the 3rd vaccination (Day 151): – Percentages of subjects with anti-HBs antibody concentrations ≥100 mIU/mL. – Anti-HBsAg GMCs. – Percentages of subjects with anti-diphtheria and anti-tetanus concentrations ≥1 IU/mL. – Anti-diphtheria and anti-tetanus antibody GMCs. – Percentage of subjects with anti-polio type 1, 2 and 3 neutralization antibody titers ≥8. • At 1 month after the 4th vaccination (Day 331): – Seroresponse, defined as post-vaccination anti-VZV virus, anti-measles virus, anti-mumps virus and anti-rubella virus antibody concentration ≥ a protective threshold^ among subjects who were seronegative (antibody concentration <assay cut-off) before vaccination.

* A 4-fold rise in hSBA titers is defined as
- if pre-vaccination titer <Limit of Detection (LOD), then a post-vaccination titer ≥ 4 times the LOD or ≥ LLOQ, whichever is greater;
- if pre-vaccination titer is ≥LOD but <LLOQ, then a post-vaccination titer ≥4 times the LLOQ;
- if pre-vaccination titer is ≥LLOQ, then a post-vaccination titer ≥4 times the pre-vaccination titer,
where pre-vaccination titer=pre-4th dose titers (Day 301)
† The endpoints and thresholds used for evaluation of the non-inferiority criteria for DTaP-HBV-IPV and Hib vaccines can be found in Protocol Amendment 8 Table 21 and the thresholds and endpoints for evaluating the non-inferiority criteria for MMR and VV vaccines can be found in Protocol Amendment 8 Table 22.
^ Protective thresholds for analyses of anti-VZV virus, anti-VZV, anti-measles virus, anti-mumps virus and anti-rubella virus antibody concentrations are present in Section 5.3.2.
¥ Visit 7 will occur either on Day 481 (for subjects who have not yet reached the 6-month follow-up after the last dose at the time protocol amendment 7 took effect) or on Day 661 (for all other subjects).
Note 1: In the context of this study, the following are considered as RIVs at different visits:
Visit 1 and Visit 2: DTPa-HBV-IPV, HRV, Hib;
Visit 3: DTPa-HBV-IPV, Hib;
Visit 5: MMR and VV.

4. ANALYSIS SETS

4.1. Definition

4.1.1. Enrolled Set

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

4.1.2. Exposed Set

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

4.1.3. Safety Set

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

All subjects in the Exposed Set with any solicited adverse event data.

4.1.3.2. Unsolicited Safety Set (unsolicited adverse events)

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

4.1.4. Full Analysis Set (FAS) for Immunogenicity

All subjects in the Exposed Set who provide immunogenicity data at either one month after their 4th vaccination or one month after their 3rd vaccination for at least 1 antigen/strain.

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

4.1.5. Per Protocol (PP) Set for Immunogenicity

All subjects in the FAS Immunogenicity who:

- Correctly receive the vaccine (i.e., receive the vaccine to which the subjects are randomized and at the scheduled time points).
- Have no protocol deviations leading to exclusion in at least one timepoint of analyses for immunogenicity.
- Are not excluded due to other reasons defined prior to unblinding or analysis.

Examples for subjects excluded due to other reasons than protocol deviations are:

- Subjects who withdrew informed consent.

Examples for subjects excluded due to protocol deviations are:

- Subjects who did not receive all the study vaccines up to Dose 3 for primary 3 doses analyses or up to Dose 4 for the 4th dose analyses.
- who received a vaccine not specified or forbidden in the protocol up to Visit 4 for primary 3 doses or up to Visit 6 for the 4th dose.

- who received a medication/product leading to exclusion from a per-protocol analysis as listed in Protocol Section 6.7.2 up to Visit 4 for primary 3 doses or up to Visit 6 for the 4th dose.
- who presented a medical condition leading to exclusion from a per-protocol analysis as listed in Protocol Section 6.8 up to Visit 4 for primary 3 doses or up to Visit 6 for the 4th dose.
- who did not comply with the post Dose 3 (for primary 3 doses) or pre and post Dose 4 (for the 4th dose) blood sample schedule, i.e. 21 to 60 days post the vaccination.
- who had no immunogenicity results post Dose 3 (for primary 3 doses) or post Dose 4 (for the 4th dose).

The allowed intervals between each study visit are given in Table 5. Subjects will not be eligible for inclusion in the per-protocol cohort for analysis of primary 3 doses if study visits are performed outside this interval up to visit 4, and they will not be eligible for analysis of the 4th dose if the study visit is performed outside this interval up to Visit 6.

Table 5 Intervals Between Study Visits

Interval	Optimal length of interval	Allowed interval[1,2]
Visit 1→ Visit 2	60 days	29 days - 81 days
Visit 2 → Visit 3	60 days	29 days - 81 days
Visit 3 → Visit 4	30 days	21 days - 60 days
Visit 3 → Visit 5	180 days	173 days - 271 days
Visit 5 → Visit 6	30 days	21 days - 60 days
Visit 5 → Visit 7 (Study termination)[3]	180 days	173 days – 201 days
Visit 5 → Visit 7 (Study termination)	360 days	353 days - 381 days

[1]The investigator should arrange study visits within this interval as subjects may not be eligible for inclusion in the PPS cohorts if they make the study visit outside this interval. All visits and windows should be planned to use the day of last vaccination as the reference point.
[2]The allowed intervals have been modified in keeping with ACIP guidelines to facilitate the safe scheduling of study visits during the COVID-19 pandemic situation.
[3] For subjects who have not yet reached the 6-month safety follow-up after the last dose at the time protocol amendment 7 took effect, Visit 7 will occur on Day 481.

4.1.6. Other Analysis Sets

Not applicable.

4.1.7. Subgroups

The following descriptive analyses will be performed by gender, race, ethnic origin and age group (6-8 weeks or ≥8 weeks) for the following parameters:

- GMCs for PCV at one month after the 3rd and 4th vaccination in Group MenB+PCV and Group Placebo+PCV.
- Percentages of subjects with hSBA titers ≥LLOQ; for each of the 4 rMenB+OMV NZ test strains and for all strains combined at each timepoint that a blood sample result will be available in Group MenB+PCV and Group Placebo+PCV.

- Percentages of subjects with hSBA titers ≥ 8 (for strains M14459, NZ98/254, M13520) and ≥16 (for strain 96217); for each of the 4 rMenB+OMV NZ test strains and for all strains combined at one month after the 4th vaccination in Group MenB+PCV and Group Placebo+PCV

Analyses will be performed on the FAS.

4.2. Criteria for eliminating data from Analysis Sets

Elimination codes are used to identify subjects to be eliminated from analysis. Details are provided below for each set.

4.2.1. Elimination from Exposed Set (ES)

Code 1030 (Study vaccine not administered at all), code 900 (invalid informed consent), and code 800 (fraudulent data) will be used for identifying subjects eliminated from ES.

4.2.2. Elimination from Solicited Safety Set

A subject will be excluded from the Solicited Safety Set analysis under the following conditions:

Code	Condition under which the code is used
2160	Subject did not provide any post-vaccination solicited safety data

4.2.3. Elimination from Unsolicited Safety Set

A subject will be excluded from the Unsolicited Safety Set analysis under the following conditions:

Code	Condition under which the code is used
2150	Subject did not provide any post-vaccination unsolicited safety data

4.2.4. Elimination from Per-protocol analysis Set (PPS)

4.2.4.1. Excluded subjects

A subject will be excluded from the PPS analysis under the following conditions

Code	Condition under which the code is used
800	Fraudulent data
900	Invalid informed consent
1030	Study vaccine not administered at all
1050	Randomization failure
1060	Randomization code was broken
1070	Subjects got vaccinated with the correct vaccine but containing a lower volume
1070	Vaccination not according to protocol (wrong site to be evaluated case-by-case, wrong route)

Code	Condition under which the code is used
1080	Vaccine temperature deviation
1090	Expired vaccine administered
2010	Protocol violation (inclusion/exclusion criteria)
2040	Administration of any medication forbidden by the protocol
2080	Subjects did not comply with vaccination schedule (missed or out of window of any study vaccination)
2090	Subjects did not comply with blood sample schedule
2100	Serological results not available (blood draw not performed, no results back from the lab)
2120	Obvious incoherence or abnormality or error in data
2130	Central/internal/external lab deviations

4.2.4.2. Right censored Data

Data from a subject will be censored from visit x for the FAS and PPS analysis under the following conditions. The code ****.X+ will also be used to identify study withdrawal from visit x.

Code	Condition under which the code is used
1060.x+	Randomization code was broken
1070.x+	Vaccination not according to protocol

4.2.4.3. Visit-specific censored Data

Data from visit x will be censored for the FAS and PPS analysis under the following conditions.

Code	Condition under which the code is used
1070.X	Subjects got vaccinated with the correct vaccine but containing a lower volume
	Vaccination not according to protocol (wrong site to be evaluated case-by-case, wrong route)
1080.X	Vaccine temperature deviation
1090.X	Expired vaccine administered
2040.X	Administration of any medication forbidden by the protocol
2080.X	Subjects did not comply with vaccination schedule (missed or out of window of any study vaccination)
2090.X	Subjects did not comply with blood sample schedule at visit x
2100.X	Serological results not available (blood draw not performed, no results back from the lab)
2120.X	Obvious incoherence or abnormality or error in data
2130.X	Central/internal/external lab deviations
2150.X	Subject did not provide any post-vaccination unsolicited safety data
2160.X	Subject did not provide any post-vaccination solicited safety data

4.2.4.4. Vaccine-specific censored Data

Data from vaccine x will be censored for the FAS and PPS analysis under the following conditions:

a. Bexsero/Placebo

b. Prevnar 13 / Prevnar 20

c. Pediarix

d. Hiberix

e. MMR

f. Varivax

Code	Condition under which the code is used
1070.X	Subjects got vaccinated with the correct vaccine but containing a lower volume
	Vaccination not according to protocol (wrong site to be evaluated case-by-case, wrong route)
2080.X	Subjects did not comply with vaccination schedule (missed or out of window of any study vaccination)

4.3. Important protocol deviation not leading to elimination from per-protocol analysis set

Not applicable

5. STATISTICAL ANALYSES

Note that standard data derivation rule and statistical methods are described in Annex 1 and will not be repeated below.

Subjects who received PCV20 at Visit 5 are analysed together with the subjects who received PCV13. Sensitivity analyses will be performed on immunogenicity analyses excluding subjects who received PCV20 as described in Section 5.3.2.1.

5.1. Demography

5.1.1. Analysis of demographics/baseline characteristics planned in the protocol

Descriptive statistics (mean, standard deviation, median, minimum, and maximum) for age (at enrolment, for the Enrolled Set and at first vaccination, for the Exposed Set) and for height and weight at enrolment will be calculated overall and by vaccine group.

Distributions of subjects by sex, race, ethnic origin, geographic region and age group (6-8 weeks or ≥8 weeks) will be summarized overall and by vaccine group.

5.1.2. Additional considerations

The number of subjects with suspected, probable or confirmed COVID-19 infection will be summarized by vaccine group and across diagnoses. This summary will be provided for the Exposed Set.

The number of exposed participants who discontinued the study will be tabulated by vaccine group with the reason for discontinuation. The summary table will be produced by relationship to COVID-19.

A summary table of important protocol deviations by relationship (related/not related) to COVID-19 will be provided.

5.2. Exposure

5.2.1. Analysis of exposure planned in the protocol

The frequencies and percentages of subjects with vaccinations will be summarized by vaccine group, vaccination number and overall. Data will be tabulated for the Exposed Set.

5.2.2. Additional considerations

Not applicable.

5.3. Immunogenicity

5.3.1. Analysis of immunogenicity planned in the protocol

The primary population for the primary and secondary immunogenicity analyses will be the PPS. All primary and selected secondary immunogenicity analyses (NI assessments for other RIVs) will be repeated on the FAS. Detail on selected Tables will be given in OPS.

5.3.1.1. Within groups assessment

For each study group the following endpoints will be assessed related to MenB strains and PCV13 strains:

- the percentage of subjects with hSBA titers ≥ LLOQ for each of the M14459, 96217, NZ98/254 and M13520 test strains and for all strains combined, at each timepoint that a blood sample result will be available
- the percentage of subjects with hSBA titers ≥5, ≥8 and ≥16 for each of the M14459, 96217, NZ98/254 and M13520 test strains, at each timepoint that a blood sample result will be available
- the percentages of subjects with hSBA titers ≥8 for each of the test strains (M14459, NZ98/254 and M13520), ≥16 for test strain 96217, and for all strains combined (composite endpoint) at one month after the 4th vaccination

- the percentage of subjects with 4-fold increase at post-4th (from pre-4th vaccination) for each of the M14459, 96217, NZ98/254 and M13520 test strains
- GMCs/GMTs and within group GMRs (for post-4th versus pre-4th titers) will be tabulated for antibodies for each antigen, at each timepoint that a blood sample result will be available
- Percentage of subjects with serum pneumococcal anti-capsular polysaccharide IgG ≥0.35 μg/mL at one month after the 3rd and 4th vaccination in Group MenB+PCV and Group Placebo+PCV.

The CIs will be calculated as 2-sided 95% for exploratory objectives and will be calculated at given alpha at the testing step for the primary objectives that are associated with statistical hypothesis testing.

Endpoints associated with the other RIV will be assess within-group as specified in Section 3. The 2-sided 95% CIs will be calculated.

5.3.1.2. Between groups assessment

For PCV antigens, at blood sampling timepoint one month post 3rd and one month post 4th vaccination and for each antibody for which results are available, for Diphtheria, Tetanus, Pertussis and Hepatitis B antigens, at blood sampling timepoint one month post 3rd vaccination, for VV and MMR, at blood sampling timepoint one month post 4th vaccination and for each antibody for which results are available:

- The CIs of the between-group GMC ratios (i.e. study group minus control group) will be computed using an analysis of variance (ANOVA) model on the logarithm10 transformation of the concentrations.

For Diphtheria, Tetanus, Hib, Polio and Hepatitis B antigens, at blood sampling timepoint one month after the 3rd vaccination, for VV and MMR, at blood sampling timepoint one month after the 4th vaccination and for each antibody for which results are available:

- The CIs of the between-group percentage differences (i.e. study group minus control group) will be computed.

5.3.1.3. Analysis of Primary Immunogenicity Objectives

Statistical Hypotheses

In total 23 hypotheses will be tested for the primary objectives. A stepwise statistical approach will be used for the 23 statistical tests. The hypotheses will be grouped into three families, based on the different immunogenicity objectives:

Family 1: 13 statistical hypotheses related to non-inferiority of PCV13 with rMenB+OMV NZ as measured by the GMCs of the 13 PCV13 antigens, after the 3rd vaccination.

Family 2: 5 statistical hypotheses related to sufficiency objective on percentage of subjects with hSBA titers ≥ 8 (for strains M14459, NZ98/254, M13520) and ≥16 (for strain 96217) at one month post 4th dose, and the composite endpoint

Family 3: 5 statistical hypotheses related to sufficiency objective on percentage of subjects with hSBA titers ≥ LLOQ at one month post 3rd dose for each of the four strains M14459, 96217, NZ98/254, and M13520, and the composite endpoint

Each family of hypotheses is linked to an objective, as follows:

- Family 1 is related to the "immunological non-inferiority of rMenB+OMV NZ + PCV13 compared to PCV13 after the 3rd vaccination" objective.

- Families 2 and 3 are related to the *"sufficiency of the immune response to rMenB+OMV NZ"* objective at one month post 4th dose and one month post 3rd dose, respectively.

The statistical hypotheses for each and all families are formulated as below:

***Family 1**: Non-inferiority of rMenB+OMV NZ + PCV13 to PCV13 with respect to GMCs at one month post 3rd vaccination*

Non-inferiority will be claimed if the following null hypothesis will be rejected for the 13 PCV13 antigens:

H_{01j}: $\mu_{Aj} - \mu_{Bj} \leq \delta$ vs. H_{11j} : $\mu_{Aj} - \mu_{Bj} > \delta$, j=1,..13,

where δ denotes the non-inferiority margin (log10(0.5)), μA, and μB denote the means of log 10-transformed concentrations at one month after the 3rd vaccination from Group MenB+PCV and Group Placebo+PCV, respectively, and j refers to the 13 antigens.

***Family 2:** Percentage of subjects with hSBA titers ≥ 8 (for strains M14459, NZ98/254, M13520) and ≥ 16 (for strain 96217) and the composite endpoint, at one month post-4th vaccination*

Sufficiency will be claimed for each of the 4 test strains and the composite endpoint, separately, if the following null hypothesis will be rejected:

H_{02j}: $P_{Aj} < A_j$ vs. H_{12j} : $P_{Aj} \geq A_j$,

where P_{Aj} denotes the percentage of subjects with hSBA titers ≥ 8 (for strains M14459, NZ98/254, M13520) and ≥16 (for strain 96217) at one month after the 4th vaccination for strain j, (j=1, 2, 3, 4, and composite). Aj represents the level of sufficient immune response for each of the four strains and composite endpoint. The immune response at one month following the 4th vaccination, will be sufficient for rMenB+OMV against each individual strain if the lower limit of the alpha-adjusted CI for the percentage of subjects with hSBA titers ≥ 8 (for strains M14459, NZ98/254, M13520) and ≥16 (for strain 96217) is ≥75% for the individual N. meningitidis serogroup B test strains, and is ≥65% for the composite endpoint.

Family 3: *Percentage of subjects with hSBA≥LLOQ for each of the four strains (M14459, 96217, NZ98/254, M13520) and the composite endpoint, post-3rd, one month post post-3rd. vaccination*

Sufficiency will be claimed for each of the 4 strains and the composite endpoint, separately, if the following null hypothesis will be rejected:

$H_{03j} : P_{Aj} < A_j$ vs. $H_{13j} : P_{Aj} \geq A_j$,

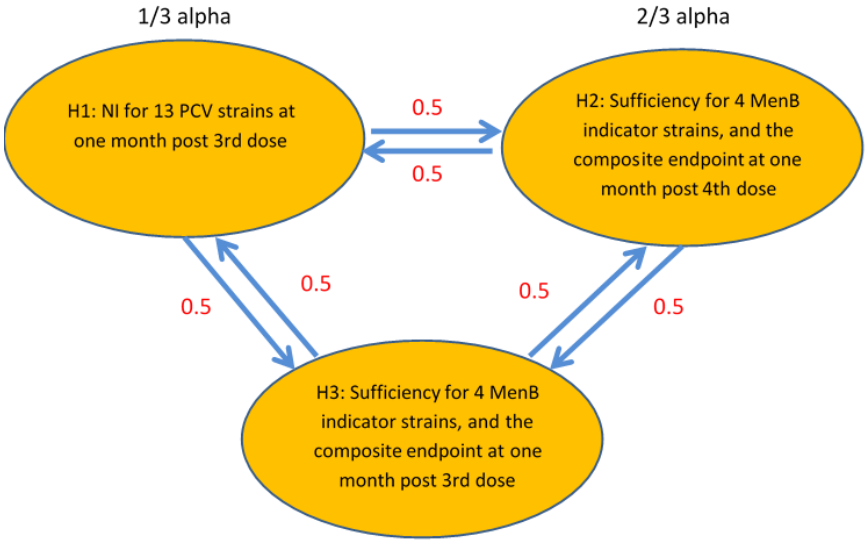
where P_{Aj} denotes the percentage of subjects hSBA≥LLOQ at one month after the 3rd vaccination for strain j, j=1, 2, 3, 4, and composite. Aj represents the level of sufficient immune response for each of the four strains and composite endpoint. The immune response at one month following the 3rd vaccination, will be sufficient for rMenB+OMV NZ against each individual strain if the lower limit of the alpha-adjusted CI for the percentage of subjects with hSBA titer ≥LLOQ is ≥60% for the N. meningitidis serogroup B test strains, and ≥50% for the composite endpoint.

Statistical Methods

For statistical analyses of the concentration/titer data, the concentrations/titers will be logarithmically transformed (base10), to fulfil Gaussian distribution assumption.

The Global Type I error rate will be controlled globally at a 5%/2.5% level (2-/1-sided, respectively). If applicable, the α-level will be propagated as described below [Bretz et al., 2009]. The sequence of testing the different families is presented in Figure 2 and described in more detail thereafter.

Figure 2 Testing Strategy for Three Families with Corresponding α Propagation



The initial α is 0.0167 (2-sided) for Family 1 and 0.0333 (2-sided) for Family 2, while it is zero for family 3.

Step 1: Family 1 and Family 2

i. Start test Family 1 and Family 2 as the first step.

- For testing Family 1 the hypotheses per antigen the p-values will be obtained from an ANOVA model, with vaccination group and center as independent variables and log transformed titers/concentrations as response variable.
- The null hypotheses will be rejected if the p-values < FWER for all thirteen antigens.
- For testing Family 2, if the lower limits of the 2-sided 96.67% CIs are greater or equal to the sufficiency margins for each of the four strains and composite endpoint, then Family 2 is successful. Otherwise, Family 2 fails.

ii. If Family 1 had succeeded and Family 2 not, then propagate ½ FWER from Family 1 to Family 3 and the other ½ FWER to Family 2, and re-test Family 2 with the new FWER which is the sum of the original FWER from Family 2 plus the ½ of FWER from Family 1. If the null hypothesis were rejected during the 2nd time test, then claim the success of Family 2 and propagate full FWER to Family 3; otherwise Family 2 fails and proceed with Family 3 testing with the ½ of FWER propagated from Family 1.

iii. If Family 2 had succeeded and Family 1 not, then propagate ½ FWER from Family 2 to Family 3 and the other ½ FWER to Family 1, and re-test Family 1 with the new FWER which is the sum of the original FWER from Family 1 plus the ½ of FWER from Family 2. If the null hypothesis were rejected during the 2nd time test, then claim the success of Family 1 and propagate full FWER to Family 3; otherwise Family 1 fails and proceed with Family 3 testing with the ½ of FWER propagated from Family 2.

iv. If both Family 1 and Family 2 had succeeded, then the FWER from both families were propagated to Family 3, and proceed to test Family 3;

v. If both Family 1 and Family 2 had failed, then no FWER will be propagated to Family 3, and we stop the testing globally and success can be claimed on none of the three families.

Step 2: Family 3

If all null hypotheses are rejected, then propagate 1/2 FWER to Family 1 and Family 2 respectively, and success can be claimed for Family 3, as well as for Family 1 and/or Family 2 whichever was successful in Step 1; otherwise stop testing globally, and success can be claimed for Family 1 and/or Family 2 whichever was successful in Step 1.

Step 3: Family 1 or Family 2

In case one of Family 1 and Family 2 failed in step 1, with the alpha passed down by Family 3, it is possible to re-test the family that failed once and again test it with ½ FWER from Family 3. If all null hypotheses are rejected, then success can be claimed for this family as well.

5.3.1.4. Analysis of Secondary Immunogenicity Objectives

The statistical hypotheses associated with the non-inferiority tests in the secondary immunogenicity objectives are described as below:

$H_0 : \mu_A - \mu_B \leq \delta$ vs. $H_{1j} : \mu_A - \mu_B > \delta$

Where δ denotes the non-inferiority margin, and μA, and μB denote either the means of log 10-transformed concentrations/titers or the percentage of subjects achieving the threshold response for binary variables.

Note that statistical hypotheses testing is not applicable for the seroresponse rates of antigens tested for Polio, MMR and VV vaccines. Instead, descriptive analysis will be performed. For each antigen tested, the percentage of subjects with anti-polio type 1, 2 and 3 neutralization antibody titers ≥8, or the percentage of subjects with post-vaccination anti-measles, anti-rubella, anti-mumps and anti-VZV virus antibody concentration ≥ a protective threshold (see protocol table 22) will be presented as point estimates along with the associated 2-sided 95% Clopper-Pearson CIs.

Statistical Methods

Concentration and titer data will be summarized by vaccine group, strain and time point. Additionally, within-subject GMRs will be computed for GMTs at one month after 4th vaccination versus pre-4th vaccination. As for GMTs/GMCs, the GMRs/GMCs and 95% CIs will be computed by exponentiating (base 10) the corresponding means and 95% CIs from an ANOVA model.

For the binary variables, for example, percentage of subjects with hSBA titer ≥ LLOQ, percentage of subjects with serum pneumococcal anti-capsular polysaccharide IgG ≥0.35 μg/ml, the number and percentage of subjects and associated 2-sided 95% Clopper-Pearson CIs (available in SAS Procedure PROC FREQ, [Frank, 2009 ;Clopper, 1934]) will be computed for each antigen/strain by vaccine group and by time-point.

Between group-differences with 95% CIs will also be derived using the Miettinen and Nurminen method [Miettinen, 1985].

5.3.2. Additional considerations

The log10-transformed antibody titers/concentrations at one month after the 3rd, pre-4th, and one month after the 4th vaccination will be analysed using an additive two-way Analysis of Variance (ANOVA) model which includes the vaccine-group effect, and a center effect. Summary tables will show adjusted geometric mean titers (GMTs) and/or geometric mean concentrations (GMCs) and adjusted ratios of GMTs / GMCs for each vaccine group.

Binary data tables will show unadjusted percentages and adjusted “between-group” differences (adjusted for center). The Miettinen and Nurminen method [Miettinen, 1985] will be applied.

Descriptive summary statistics will be provided for subgroups gender, race, ethnic origin and age group (6-8 weeks or ≥8 weeks), for the following parameters:

- GMCs for PCV at one month after the 3rd and 4th vaccination.
- Percentages of subjects with hSBA titer ≥ LLOQ; for each of the 4 rMenB+OMV NZ test strains and for all strains combined, at each timepoint that a blood sample result will be available, in Group MenB+PCV and Group Placebo+PCV.
- Percentages of subjects with hSBA titers ≥ 8 (for strains M14459, NZ98/254, M13520) and ≥16 (for strain 96217); for each of the 4 rMenB+OMV NZ test strains and for all strains combined at one month after the 4th vaccination in Group MenB+PCV and Group Placebo+PCV.

Subgroup analyses will be performed on the FAS.

The MenB serum bactericidal assay (hSBA) limits to be applied to the analyses will be as follows:

Assay	LOD	LLOQ
M14459 (fHbp)	4	5
96217 (NadA)	6	14
NZ98/254 (PorA)	4	6
M13520 (NHBA)	4	6

Seroresponse for varicella will be defined as post-vaccination anti-VZV gE IgG concentration ≥300 mIU/mL among subjects who were seronegative (antibody concentration < assay cut-off) before vaccination. The assay cut-off will be the LLOQ = 97.0 mIU/mL (anti-gE ELISA).

Seroresponse of MMR will be defined as post-vaccination anti-measles virus, anti-mumps virus and anti-rubella virus antibody concentration ≥ a protective threshold among subjects who were seronegative (antibody concentration <assay cut-off) before vaccination (MMR Luminex assay).

Thresholds and cut-off values are presented below:

	Measles (mIU/mL)	Mumps (AU/mL)	Rubella (IU/mL)
Threshold	116	296	24
Cut-off = LLOQ	29.082	189.240	1.916

5.3.2.1. Sensitivity analyses due to the administration of PCV20 at Visit 5

The following analyses will be performed excluding subjects who did receive PCV20 at Visit 5:

- Numbers and percentages of subjects with hSBA titers ≥ 8 (for strains M14459, NZ98/254, M13520) and ≥16 (for strain 96217) for each of the 4 rMenB+OMV NZ

test strains and for all strains combined (composite endpoint) at one month after the 4th vaccination in Group MenB+PCV and Group Placebo+PCV with their associated 2-sided 95% Clopper-Pearson CIs.

- ECL GMCs for each of the 13 PCV13 antigens with their 2-sided 95% CIs at one month after the 4th vaccination in Group MenB+PCV and Group Placebo+PCV.
- Numbers and percentages of subjects with serum pneumococcal anti-capsular polysaccharide IgG ≥0.35 µg/mL for each of the 13 PCV13 antigens at one month after the 4th vaccination in Group MenB+PCV and Group Placebo+PCV with their associated 2-sided 95% Clopper-Pearson CIs.
- Between-group GMC ratios (i.e. study group minus control group) against measles, mumps, rubella and VZV antigens at one month after the 4th vaccination with their associated 2-sided 95% CIs.
- Numbers and percentages of subjects with hSBA titers ≥LLOQ for each of the M14459, 96217, NZ98/254 and M13520 test strains at one month after the 4th vaccination in Group MenB+PCV and Group Placebo+PCV with their associated 2-sided 95% Clopper-Pearson CIs.
- Numbers and percentages of subjects with hSBA titers ≥5 for each of the M14459, 96217, NZ98/254 and M13520 test strains at one month after the 4th vaccination in Group MenB+PCV and Group Placebo+PCV with their associated 2-sided 95% Clopper-Pearson CIs.
- hSBA GMTs and within group geometric mean ratios (GMRs) for post 4th vaccination over pre-4th vaccination against each of the M14459, 96217, NZ98/254 and M13520 test strains.
- Numbers and percentages of subjects with 4-fold increase in hSBA titers (at post 4th vaccination from pre-4th vaccination) for each of the M14459, 96217, NZ98/254 and M13520 test strains.

5.4. Safety

5.4.1. Analysis of safety planned in the protocol

Distribution of subjects by vaccinations will be summarized by vaccine group for the Exposed Set. The primary analysis will be performed on the Solicited / Unsolicited Safety Set.

5.4.1.1. Within groups assessment

Analysis of Solicited Adverse events

All solicited AEs will be summarized according to defined severity grading scales, see Table 6 and Table 7.

Table 6 Grading of Solicited Local Adverse Events (administration site events) for All Subjects

Adverse Events	Grading of Severity			
	Grade 0	Mild	Moderate	Severe
Tenderness or discomfort to touch at injection site	None	Minor light reaction to touch	Cried or protested to touch	Cried when injected limb was moved
Hardness of skin at the injection site	0 mm	1 - 25 mm	26 - ≤50 mm	>50 mm
Swelling of skin at the injection site				
Redness at injection site				

Table 7 Grading of Solicited Systemic Adverse Events for All Subjects

Adverse Events	Grading of Severity			
	Grade 0	Mild	Moderate	Severe
Decreased eating	None	Eating less than normal for 1 - 2 feeds/ meals	Missed 1 or 2 feeds / meals	Missed more than 2 feeds/ meals
Increased sleepiness	None	Shows an increased drowsiness	Sleeps through feeds/ meals	Sleeps most of the time and it is hard to arouse him/her
Vomiting / throwing up	None	1-2 times in 24 hours	3 – 5 times in 24 hours	6 or more times in 24 hours or requires intravenous hydration
Loose stools / 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
Irritability	None	Requires more cuddling and is less playful than usual	More difficult to settle	Unable to console
Persistent / continuous crying	None	Crying less than 1 hour	Crying for 1 up to 3 hours	Crying for 3 or more hours
Rash[1]	0	1-50 lesions	51-150 lesions	>150 lesions
Parotid/salivary gland swelling[1]	None	Swelling without difficulty moving the jaw	Swelling with difficulty moving the jaw	Swelling with accompanying general symptoms
Fever[2]	<38.0°C (<100.4°F)	≥38.0 - 38.9°C (≥100.4 – 102.1°F)	≥39.0 - 39.9°C (≥102.2 – 103.9°F)	≥40.0°C (≥ 104.0°F)

[1]Rash and parotid/salivary gland swelling will be recorded only after receiving the MMR and VV vaccines at 12 months of age at Visit 5 (Day 301). These specific systemic AEs, along with fever, will be recorded for 30 days following the MMR and VV vaccine administration.

[2]Preferred locations for measuring temperature are the rectum for subjects <12 months of age and the axilla for subjects ≥12 months of age. Body temperature is to be recorded daily, ideally at the same time each day.

Frequencies and percentages of subjects (with 95% CI; [Frank, 2009; Clopper, 1934]) experiencing each AE will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic AE overall and at each time point will also be presented.

Post-vaccination solicited AE reported from Day 1 to Day 7 will be summarized for the interval Day 1-7 (and Day 1-3, Day 4-7 if needed) by maximal severity and by vaccine

group, excluding the 30-minute measurement, which will be summarized separately. For MMR and VV-specific solicited systemic AEs (parotid/salivary gland swelling, fever, rash) collected after Visit 5 (30 minutes through Day 30 post vaccination), the study period will be divided into the following intervals: 6 hours through Day 7, Day 8 through Day 30.

The severity of solicited local AEs (administration site events), including redness at injection site, swelling of skin at injection site, and hardness of skin at injection site will be summarized according to categories based on linear measurement: None (0 mm); Mild (1 mm to 25 mm); Moderate (26 mm to 50 mm); Severe (> 50mm).

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

Fever, derived from measured body temperature (≥ 38.0°C/100.4°F), will be summarized according to “Grade 0 (none)” (< 38.0°C), “mild “(≥ 38.0 - 38.9°C), “moderate” (≥ 39.0 - 39.9°C) and “severe” (≥ 40.0°C).

Each solicited local (administration site) and systemic AE will also be further summarized as “none” versus “any” (for fever the latter will be ≥38.0°C/100.4°F).

Use of antipyretics and analgesics will be summarized by type of use (prophylactic versus treatment) and percentage of subjects (with 95% CI) reporting use.

Body temperature will be summarized by 0.5°C increments from 36.0°C up to ≥40°C and will be broken down according by route of measurement, if applicable. Frequencies and percentages of subjects (with 95% CI) with temperatures ≥38.0°C and temperatures ≥40.0°C will also be presented.

Descriptive summary statistics will be provided for subgroups gender, race, and ethnic origin.

Analysis of Unsolicited Adverse Events

This analysis applies to all AEs occurring during the study, judged either as reasonable possibly related, or not reasonable possibly related to vaccination by the investigator, recorded in AE eCRF, with a start date on or after the date of first vaccination. All AEs starting prior to the first vaccination will only be listed. The original verbatim terms used by investigators to identify AEs in the eCRFs will be mapped to preferred terms using the MedDRA dictionary. The AEs will then be grouped by MedDRA preferred terms into frequency tables (with 95% CI; [Frank, 2009; Clopper, 1934]) according to system organ class.

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

Serious adverse events, withdrawal due to AEs and AESIs will be described in detail.

Separate summaries will be produced for the following categories:

- Serious adverse events (SAE)
- Adverse events related to vaccine
- Adverse events of special interest (pIMDs, seizures, and/or arthritis)
- Adverse event leading to withdrawal with relationship to COVID-19
- Adverse events leading to a medically attended visit

These summaries will also be presented by the 0-6/0-12 months safety follow-up periods after the last study vaccination.

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

Descriptive summary statistics will be provided for subgroups gender, race, ethnic origin and age group (6-8 weeks or ≥8 weeks), for the following parameters:

- Adverse events
- Adverse events related to vaccine
- Serious adverse events (SAE)
- Adverse events leading to a medically attended visit

In cases needed, a few specific AEs and SAEs (for example AESI) will be analysed statistically using Poisson regression, where the total number of days for which the subject was followed-up (excluding any pre-vaccination periods) will be used as an offset. The Poisson regression enables calculation of the risk ratio (RR) of a SAE or AESI, including 2-sided 95% CI, for each preferred term. Confidence intervals of RRs will not be adjusted for multiplicity. i.e., owing to the possible large number of comparisons it cannot be ruled out that potential safety signals occur by chance alone.

```
PROC GENMOD  DATA = <dataset name>;
   CLASS   ARMCD  SITEID;
   MODEL   AVAL = ARMCD SITEID / DIST = POISSON OFFSET = log(TIME) LINK
= LOG;
   ESTIMATE  'Beta A/B'  ARMCD  1 -1  / EXP;

RUN;
```

*time: number of days the subject was followed-up;

5.4.1.2. Between groups assessment

95% CIs for differences between vaccine groups will be provided according to Miettinen and Nurminen method [Miettinen, 1985].

5.4.2. Additional considerations

5.4.2.1. Exclusion of implausible solicited Adverse Event

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 8 Implausible Solicited Adverse Events

Parameter	Implausible measurements
Body temperature	≤ 33°C or ≥ 42°C
Erythema	Measurements < 0 mm or ≥ 450 mm
Induration	Measurements < 0 mm or ≥ 250 mm
Swelling	Measurements < 0 mm or ≥ 250 mm

5.4.2.2. Duration of Solicited Adverse Events

Duration of a solicited adverse event will be calculated as follows: *end date – start date + 1*. The duration will be derived assuming that the solicited adverse event occurred continuously from the first day to the last day the event was reported regardless of how many days the event was documented in between.

Statistics (i.e. mean, median minimum, maximum, quartiles) on the duration in days of solicited local (administration site) and systemic adverse events post vaccination will be reported by timepoint and overall, by each solicited reaction, for each vaccine group.

Statistics (i.e. mean, median minimum, maximum, quartiles) on the duration in days of solicited local (administration site) and systemic adverse events post any vaccination will be reported by each solicited reaction, for each vaccine group.

Statistics (i.e. mean, median minimum, maximum, quartiles) on the day of onset of solicited local (administration site) and systemic adverse events post vaccination will be provided by timepoint, by each solicited reaction, for each vaccine group.

Statistics (i.e. mean, median minimum, maximum, quartiles) on the day of onset of solicited local (administration site) and systemic adverse events post any vaccination will be provided by each solicited reaction, for each vaccine group.

5.4.2.3. Derivation rule for duplicates Solicited Adverse Events

If there are two reported assessments for the same solicited adverse event in FACE, the Investigator one will be used for the analysis.

5.4.2.4. Combined Solicited and Unsolicited Adverse Events

The number (%) 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 as per the following codes:

Local reactions

Solicited symptom	Lower level term code	Corresponding Lower level term decode
INDURATION	10060708	Induration
SWELLING	10053425	Swelling at injection site
REDNESS	10022098	Redness at injection site
TENDERNESS	10043224	Tenderness

Systemic reactions

Solicited symptom	Lower level term code	Corresponding Lower level term decode
CHANGE IN EATING HABITS	10063889	Oral intake reduced
SLEEPING MORE THAN USUAL	10020765	Hypersomnia
VOMITING	10047700	Vomiting
DIARRHOEA	10012727	Diarrhea
IRRITABILITY	10057224	Irritability post vaccinal
UNUSUAL CRYING	10011470	Crying abnormal
RASH	10037844	Rash
PAROTID GLAND swelling	10034028	Parotid swelling
FEVER	10016558	Fever

For clinicaltrials.gov and EudraCT posting purposes, a summary of combined solicited and unsolicited non-serious adverse events will be produced by System Organ Class and preferred terms and according to occurrence of each event.

5.4.2.5. Immediate Unsolicited Adverse Events

The numbers and percentages of subjects who reported at least one immediate unsolicited adverse event (reactions that occurred during the first 30 minutes) post vaccination will be provided by timepoint, for each vaccine group.

5.4.2.6. Clinical Safety Laboratory Investigations

Not applicable

5.4.2.7. Concomitant Medication and Vaccination

Medications will be coded using the GSKDRUG dictionary. The frequencies and percentages of subjects starting concomitant medications during 30 days post vaccination will be tabulated by vaccine group.

Any concomitant vaccination administered in the period starting from birth and ending at the last study visit (Day of birth to Day 481 or Day 661), and any non-study concomitant vaccination (see Protocol Amendment 8 Section 6.1.2), are being recorded according to Protocol and to be tabulated.

5.4.2.8. e-Diary Considerations

For participants who have more than one solicited local (i.e., injection site redness, hardness of skin, swelling of skin, tenderness or discomfort to the touch) or systemic (i.e., fever [temperature ≥ 38.0°C], decreased eating, increased sleepiness, vomiting/throwing up, loose stools/diarrhea, irritability, persistent/continuous crying, rash, parotid/salivary gland swelling) measurement on a day, all data is listed. For the analysis, the worst measurement is analysed. For example, if for a participant a temperature of 38.5°C and 39.0°C is recorded on one day, both values get listed, for the analysis the 39.0°C is analysed.

5.4.2.9. e-Diary Compliance Analyses

Averages of percentages of e-Diary entries will be reported by timepoint for each vaccine group. Percentages of e-Diary entries will be calculated at participant level, by timepoint, as number of days e-Diary was entered divided by 7 or by 30, for Visit 5 timepoint.

Numbers and percentages of subjects who provided e-Diary entries for all the solicited local (administration site) and systemic adverse events during the 7 days post vaccination (including the day of vaccination and excluding the 30-minute measurement) will be presented by timepoint, by each reporting day, by each solicited reaction, for each vaccine group.

Numbers and percentages of subjects who provided e-Diary entries during all 7 days post vaccination (including the day of vaccination and excluding the 30-minute measurement) for all the solicited local (administration site) and systemic adverse events will be presented by timepoint, for each vaccine group.

Numbers and percentages of subjects who provided e-Diary entries consecutively during the three days (day 1 through day 3) post-vaccination, five days (day 1 through day 5) post-vaccination and seven days (day 1 through day 7) post-vaccination, for all the solicited local (administration site) and systemic adverse events, will be reported by timepoint, by each solicited reaction, for each vaccine group.

Numbers and percentages of subjects who provided e-Diary entries consecutively during seven days (day 1 through day 7) post-vaccination, and consequently weekly till day 30 post-vaccination, for all the solicited local (administration site) and systemic adverse events, will be reported for Visit 5, by each solicited reaction, for each vaccine group.

6. ANALYSIS INTERPRETATION

The primary objective is divided in two parts: safety and immunogenicity. The endpoints regarding safety objective will be only descriptive. The immunogenicity endpoints are further divided into 3 families.

Section 5.3.1.3 describes how the analyses related to the primary immunogenicity objectives should be interpreted, and Figure 2 explains how the Global Type I error rate will be controlled at 5% two sided among the 3 families. Section 5.3.1.4 describes the analysis related to the secondary immunogenicity objectives.

7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

Description	Analysis ID	Disclosure Purpose (CTRS=public posting, SR=study report, internal)	Dry run review needed (Y/N)	*Study Headline Summary (SHS)*requiring expedited communication to upper management (Yes/No)	Reference for TFL
Analysis of all epochs	E1_0X	Study report	Yes	Yes	All tables from TFL

Final analyses will be conducted on data as clean as possible.

8. CHANGES FROM PLANNED ANALYSES

Definition of PPS has been modified as follows: if the subject will be free from deviations in at least one timepoint of analyses for immunogenicity, subject will be considered as part of PPS.

The descriptive analyses by subgroup (i.e. by gender, race, ethnic origin and age group 6-8 weeks or ≥8 weeks) will be performed on the parameter GMCs for PCV and not on GMC ratios, at one month after 3rd and 4th vaccination.

Summaries of serious adverse events (SAE), adverse events related to vaccine, adverse events of special interest, adverse events leading to withdrawal with relationship to COVID-19, adverse events leading to a medically attended visit will be produced by the 0-6/0-12 months safety follow-up periods after the last study vaccination and not on the 0-6/6-12 months follow-up periods.

9. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

The OPS provides the list of tables/listings and figures needed for the study report. It also identifies the tables eligible for each analysis and their role (synopsis, in-text, post-text, SHS, CTRS). Note that all TFL aimed to be included as post-text are noted as post-text even if these are tabulation of individual data such as listing of SAE. The post-text material contains all source material for the study report and accordingly a post-text table may be redundant with an in-text table.

OPS is also providing the study specific mock-up tables to be used for TFLs development.

The following group names will be used in the TFLs, to be in line with the protocol and CSR:

Group order in tables	Group label in tables
1	MenB+PCV
2	Placebo+PCV

10. ANNEX 1: STANDARD DATA DERIVATION RULE AND STATISTICAL METHODS

10.1. Statistical Method References

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

Frank Bretz, Willi Maurer, Werner Brannath, Martin Posch.A graphical approach to sequentially rejective multiple test procedures. *Statistics in medicine*. 2009; 28:586–604

Miettinen O., Nurminen M. Comparative analysis of two rates. *Statistics in Medicine* 1985; **4**(2):213-226.

11. ANNEX 2: STUDY SPECIFIC MOCK TFL

OPS is available in Veeva under section 11.01.01 of the study folder.