Statistical Analysis Plan	
Detailed Title:	A phase III, randomized, controlled, observer-blind study to demonstrate effectiveness, immunogenicity and safety of GSK's meningococcal Group B and combined ABCWY vaccines when administered to healthy adolescents and young adults.
eTrack study number and Abbreviated Title	205416 [MENB REC 2ND GEN-038 (V72_72)]
Scope:	All data pertaining to the above study
Date of Statistical Analysis Plan	Amendment 9 Final: 06 Sep 2023

APP 9000058193 Statistical Analysis Plan Template V4 (Effective date: 3June2019)

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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
Eli Type	Internal database code for type of elimination code
ELISA	Enzyme-linked immunosorbent assay
EOS	End of Study
ES	Exposed Set
FAS	Full Analysis Set
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titre
GSK	GlaxoSmithKline
LL	Lower Limit of the confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
PCD	Primary completion Date
PPS	Per-Protocol Set
RR	Relative Risk
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
TFL	Tables Figures and Listings
TOC	Table of Contents

1. DOCUMENT HISTORY

Date	Description	Protocol Version
25 Jul 2019	First version	Amendment 1: 23 MAY 2019
15 Jun 2020	Amendment 1	Amendment 2: 18 MAR 2020
25 Mar 2022	Amendment 2	Amendment 4: 12 MAY 2021
25 Apr 2022	Amendment 3	Amendment 4: 12 MAY 2021
08 Sep 2022	Amendment 4	Amendment 4: 12 MAY 2021
12 Jan 2023	Amendment 5	Amendment 4: 12 MAY 2021
27 Feb 2023	Amendment 6	Amendment 4: 12 MAY 2021
14 Mar 2023	Amendment 7	Amendment 4: 12 MAY 2021
30 Aug 2023	Amendment 8	Amendment 4: 12 MAY 2021
06 Sep 2023	Amendment 9	Amendment 4: 12 MAY 2021

2. OBJECTIVES/ENDPOINTS

Table 1 Study objectives and endpoints

Objectives	Endpoints
Primary	
Vaccine effectiveness (Test-based): rMenB+OMV NZ To demonstrate the effectiveness of the rMenB+OMV NZ vaccine against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity using enc-hSBA at 1 month after the 3-dose (0,2,6-months) and 2-dose (0,6-months; 0,2-months) vaccination series when compared to 1 month after the MenACWY vaccination. *Criterion* *Lower limit (LL) of the two-sided 97.5% confidence interval (CI) for vaccine effectiveness is above 65% against a randomly selected strain panel between the:* • *MenB_0_2_6 and ACWY groups (for 0,2,6-months schedule)* • *MenB_0_6 and ACWY groups (for 0,6-months schedule),* • *MenB_0_2_6 and ACWY groups (for 0,2-months schedule)*	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at 1 month after the: • 3-dose vaccination series in MenB_0_2_6 group (Day 211, Month 7) • 2-dose vaccination series in MenB_0_6 group (Day 211, Month 7), and • 2-dose vaccination series in MenB_0_2_6 group (Day 91, Month 3) • 1 month after the MenACWY vaccination in ACWY group (Day 31, Month 1).
Effectiveness (Responder-based): rMenB+OMV NZ To demonstrate the effectiveness of the rMenB+OMV NZ vaccine by assessing the percentages of subjects whose sera kill ≥70% of strains tested using enc-hSBA at 1 month after the 3-dose (0,2,6-months) and 2-dose (0,6-months; 0,2-months) vaccination series of the rMenB+OMV NZ. *Criterion:* *LL of the two-sided 97.5% CI for the percentages of subjects whose sera kill ≥70% of strains is above 65%, tested for:* • *MenB_0_2_6 group (for 0,2,6-months schedule)* • *MenB_0_6 group (for 0,6-months schedule),*	The percentages of subjects whose sera kill ≥70% of the strains tested using enc-hSBA, at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group), • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group)

Objectives	Endpoints
• *MenB_0_2_6 group (for 0,2-months schedule)*	
The 3 vaccine schedules will be tested for both, test-based and responder-based, in a hierarchical way (starting from 0-2-6, to 0-6 and 0-2). Refer to Protocol Section 10.1 for details on continuing the evaluation.	
Lot-to-lot consistency: MenABCWY vaccine To demonstrate lot-to-lot consistency of the immune responses of 3 lots of the MenACWY component of the MenABCWY vaccine, as measured by hSBA GMTs directed against serogroups A, C, W and Y at 1 month after last vaccination (0,6-months). *Criterion:* *The two-sided 97.5% CIs^ for the ratio of hSBA GMTs of antibodies against serogroups A, C, W and Y are within the [0.5;2.0] equivalence interval for each pair of lots*.	GMTs directed against serogroups A, C, W and Y for each lot (ABCWY-1 group, ABCWY-2 group, ABCWY-3 group) at 1 month after the last vaccination (Day 211, Month 7)
Immunological non-inferiority: MenABCWY vaccine vs. MenACWY vaccine To demonstrate the immunological non-inferiority of the MenABCWY vaccine compared to the MenACWY vaccine as measured by the percentages of subjects achieving a 4-fold rise in hSBA titres against *N. meningitidis* serogroups A, C, W and Y at 1 month after the last MenABCWY vaccination (0,6-months) and 1 month after the MenACWY vaccination. *Criterion:* *LL of the 2-sided 97.5% CI^ for the group difference in percentages of subjects achieving a 4-fold rise* in hSBA titres is above -10%.*	The percentages of subjects with 4-fold rise* in hSBA titres against *N. meningitidis* serogroups A, C, W and Y at 1 month after the: • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • 1 month after the MenACWY vaccination for the ACWY group (Day 31, Month 1) relative to baseline (Day 1, Month 0).
Vaccine effectiveness (Test-based): MenABCWY vaccine To demonstrate the effectiveness of the MenABCWY vaccine against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains as measured by enc-hSBA at 1 month after the last MenABCWY vaccination (0,6-months) when compared to 1 month after the MenACWY vaccination. *Criterion:* *LL of the two-sided 97.5% CI^ for vaccine effectiveness is above 65% against a randomly selected strain panel between the ABCWY group (pooled lots) and the ACWY group.*	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at 1 month after the: • last vaccination for the ABCWY group (pooled) (Day 211, Month 7), and • 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1).
Effectiveness non-inferiority: MenABCWY vaccine vs. rMenB+OMV NZ vaccine To demonstrate the non-inferiority of the effectiveness of the MenABCWY vaccine (0,6-months schedule) compared to the rMenB+OMV NZ vaccine (0,2,6-months or 0,6-months or 0,2-months)† in terms of percentage of samples with bactericidal serum activity using enc-hSBA against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains.	The percentages of samples with bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains at 1 month after the: • last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • 3-dose vaccination series of rMenB+OMV vaccine (Day 211, Month 7 in MenB_0_2_6 group) or 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) or 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group)†

Objectives	Endpoints
Criterion: *LL of the two-sided 97.5% CI^ for the difference in percentages of samples with bactericidal serum activity using enc-hSBA against a randomly selected panel of endemic US N. meningitidis serogroup B invasive disease strains is above -5% at 1 month after:* • *the last vaccination in ABCWY group (pooled lots) (for 0,6 months schedule), and* • *The last vaccination in MenB_0_2_6 group (for 0,2,6-months schedule) or the last vaccination in MenB_0_6 group (for 0,6-months schedule) or the second vaccination in MenB_0_2_6 group (for 0,2-months schedule*	
Effectiveness (Responder-based): MenABCWY vaccine To demonstrate the effectiveness of MenABCWY vaccine by assessing the percentages of subjects whose sera kill ≥70% of strains tested using enc-hSBA at 1 month after the last vaccination of MenABCWY (0,6-months). *Criterion:* *LL of the two-sided 97.5% CI^ for the percentages of subjects whose sera kill ≥70% of strains tested for MenABCWY is above 65%.*	The percentages of subjects whose sera kill ≥70% of the strains tested using enc-hSBA, at 1 month after the last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7).
Safety To evaluate the safety and reactogenicity of the MenB, MenABCWY, and the MenACWY vaccines	• The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [body temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) adverse events (AEs) during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. • The frequencies and percentages of subjects with any unsolicited AEs (including all SAEs, AEs leading to withdrawal, AESIs and medically attended AEs) during the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. • The percentages of subjects with SAEs, AEs leading to withdrawal, AESIs and medically attended AEs throughout the study period [Month 0 to Month 18].
Secondary	
To demonstrate the immunological non-inferiority of the MenABCWY vaccine compared to the rMenB+OMV NZ vaccine as measured by the percentages of subjects achieving a 4-fold rise in hSBA titres against *N. meningitidis* serogroup B indicator strains at 1 month after the last MenABCWY vaccination (0,6-months schedule) and 1 month after the rMenB+OMV NZ vaccination (0,2,6-months or 0,6-months or 0,2-months)†	The percentages of subjects with 4-fold rise** in hSBA titres against *N. meningitidis* serogroup B indicator strains at 1 month after the: • last MenABCWY vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • 3-dose vaccination series of rMenB+OMV vaccine(Day 211, Month 7 in MenB_0_2_6 group) or 2-dose vaccination series (Day 211, Month 7 in

Objectives	Endpoints
Criterion: *Non-inferiority will be demonstrated if the LL of the 2-sided 95% CI for the group difference in percentage of subjects achieving a 4-fold rise** in hSBA titres against N. meningitidis serogroup B indicator strains is above -10%.*	MenB_0_6 group) or 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group)† relative to baseline (Day 1, Month 0).
To assess the effectiveness of the rMenB+OMV NZ and MenABCWY vaccines against each of the randomly selected endemic US *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series when compared to 1 month after the MenACWY vaccination.	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group) • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • MenACWY vaccination (Day 31, Month 1 in ACWY group).
To describe the distribution of subjects by percentages of serogroup B invasive disease strains killed using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series of rMenB+OMV NZ and MenABCWY vaccines.	The percentages of serogroup B invasive disease strains killed using enc-hSBA in each subject at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7)
To assess the immune response to the rMenB+OMV NZ (0,2,6-months, 0,6-months and 0,2-months) and MenABCWY (0,6-months) vaccines against *N. meningitidis* serogroup B indicator strains at pre-vaccination (Day 1, Month 0) and at 1 month after the last MenABCWY vaccination and at 1 month after the second and third vaccination of rMenB+OMV NZ.	The immune response to the rMenB+OMV NZ and ABCWY vaccines will be evaluated by measuring bactericidal activity against *N. meningitidis* serogroup B indicator strains as following: *1. The percentages of subjects with hSBA titres ≥ lower limit of quantitation (LLOQ) for each (individual response) and all (composite response) serogroup B indicator strains at baseline (Day 1, Month 0) and at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *2. The percentages of subjects with 4-fold rise** in hSBA titres at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group)

Objectives	Endpoints
	• 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 90, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *relative to baseline (Day 1, Month 0).* *3. hSBA GMTs at baseline (Day 1, Month 0) and at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *4. hSBA GMRs at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *relative to the baseline (Day 1, Month 0).*
To assess the immune response to MenABCWY (0,6-months schedule) and MenACWY (single dose) vaccines against *N. meningitidis* serogroups A, C, W and Y, at pre-vaccination (Day 1, Month 0) and at 1 month after the first and the last MenABCWY vaccination and 1 month after the MenACWY vaccination.	*1. The percentage of subjects with hSBA titres ≥ LLOQ for serogroups A, C, W and Y at baseline (Day 1, Month 0) and:* • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1). *2. The percentage of subjects with 4-fold rise* in hSBA titres at 1 month after the:* • first vaccination (Day 31, Month 1) for the ABCWY group (pooled lots) compared to the MenACWY vaccination in the ACWY group (Day 31, Month 1) *relative to baseline (Day 1, Month 0).* *3. hSBA GMTs against N. meningitidis serogroups A, C, W and Y* at baseline (Day 1, Month 0) and: • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1). *4.hSBA GMRs against N. meningitidis serogroups A, C, W and Y at:* • 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7)

Objectives	Endpoints
	for the ABCWY group (pooled lots) as compared to baseline (Day 1, Month 0), and • 1 month after the single MenACWY vaccination in the ACWY group (Day 31, Month 1) as compared to baseline (Day 1, Month 0). *5.The total IgG as measured by ELISA GMCs against serogroups A, C, W and Y* at baseline (Day 1, Month 0) and*:* • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1).

Abbreviations: ELISA = enzyme-linked immunosorbent assay; Enc-hSBA = endogenous complement human serum bactericidal assay; GMC = geometric mean concentrations; GMT = geometric mean titre; GMR = geometric mean ratio; CI = confidence interval; hSBA = human serum bactericidal assay; LOD: limit of detection; LLOQ = lower limit of quantitation; LL = lower limit; AE = Adverse event; SAE = Serious adverse event; AESI = Adverse event of special interest

N.meningitidis serogroup B indicator strains = M14459, 96217, M13520 and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively.

Refer to Protocol Section 10 for details on evaluation of objectives and sample size justification. Refer to Glossary of terms for definitions of test-based and responder-based effectiveness

^ If the co-primary effectiveness objectives for rMenB+OMV NZ are met, then all objectives for MenABCWY will be evaluated at 95% CI. Refer to Protocol Section 10.1 for details

P† PIf all objectives of rMenB+OMV NZ are met, the comparator will be the 0,2-months schedule. If the 0,2-months objective is not met, and the 0,6-months is met, then the 0,6-months schedule will be the comparator. If the 0,6-months is also not met, then the 0,2,6-months schedule will be the comparator.

*For the Men A, C, W, Y evaluation, the 4-fold rise is defined as:

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

**For the MenB evaluation, the 4-fold rise per each indicator strain is defined as:

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

‡ = post-2nd vaccination for 0,6 and 0,2 schedule and post-3rd vaccination for 0,2,6 schedule.

3. STUDY DESIGN

3.1. Scientific rationale for study design

As the rMenB+OMV NZ licensure in the US was issued through accelerated approval, the FDA has requested to demonstrate the effectiveness of the vaccine against an extended panel of serogroup B meningococcal strains (MenB) as a post-marketing commitment in US adolescents and young adults, thus confirming that the vaccine can protect against diverse meningococcal B strains prevalent in the United States.

The availability of a pentavalent meningococcal vaccine in a single administration would however reduce the number of injections and could increase coverage for meningococcal disease caused by *N. meningitidis* serogroups A, B, C, W, and Y worldwide. GSK's investigational MenABCWY combination vaccine is intended to protect against 5 of the most prevalent serogroups of *Neisseria meningitidis* (A, B, C, W, Y) in humans.

Hence, along with the licensed MenB vaccine (*Bexsero*), this Phase III study will also assess the safety, effectiveness, and immunogenicity of the investigational MenABCWY vaccine.

Rationale for effectiveness assessment

As mentioned above, one of the primary purposes of this study is to evaluate the effectiveness of 2 or 3 doses of rMenB+OMV NZ and of 2 doses of the MenABCWY vaccines in healthy adolescents and young adults by measuring the bactericidal activity against 110 endemic US *N. meningitidis* serogroup B strains using an endogenous complement human Serum Bactericidal Assay (enc-hSBA). Sera from the ACWY group receiving the MenACWY vaccine will also be tested against serogroup B meningococcal strains by enc-hSBA as a control for test-based effectiveness assessment. The overall vaccine effectiveness (VE) against all 110 strains combined will be computed by means of a generalised linear model. For additional details see statistical analysis section of the Clinical Study Protocol (Protocol Section 10).

Rationale for lot-to-lot consistency assessment

MenABCWY is a reconstituted vaccine with the lyophilised 'ACWY component' and liquid rMenB+OMV NZ. The MenB component has the same formulation as the commercial *Bexsero*. To demonstrate that the lots of the investigational MenABCWY vaccine are adequately representative of the formulation intended for marketing, equivalence will be assessed for 3 different lots of the ACWY component of the ABCWY vaccine.

Rationale for non-inferiority assessment of MenABCWY vs MenACWY and rMenB+OMV NZ

The study aims to also demonstrate that the investigational combination MenABCWY vaccine is not inferior to a licensed MenACWY vaccine (*Menveo*) and a licensed MenB vaccine (*Bexsero*) which are part of the current standards of care in the US for prevention of invasive disease caused by *N. meningitidis* serogroups A, C, W, Y and by *N. meningitidis* serogroup B, respectively.

Rationale for blood volume collected:

In order to provide the necessary serum volume for the bactericidal assays (enc-hSBA and/ or hSBA(s)), 25 mL whole blood will be collected at Visit 2, Visit 4 and Visit 6. At pre-vaccination (Visit 1), 20 mL whole blood will be collected to provide the necessary serum volume for the hSBA.

Blood samples are taken from all subjects irrespective of the testing status in order to maintain the study blind. Refer to Protocol Section 8.4.2.1 for further details.

Rationale for the selected vaccination schedules

rMenB+OMV NZ: This study aims at demonstrating the VE of the rMenB+OMV NZ vaccine administered as 2-dose vaccine, either with a shorter interval (0,2-months) or a prolonged interval (0,6-months) between doses. A 3-dose schedule has been also added to better characterise the VE.

Note: The rMenB+OMV NZ in the ACWY group is administered in a 0,1-months schedule. This interval is within the recommendations in the summary of product characteristics of *Bexsero* and helps in maintaining the blind. No objectives are associated with this schedule of rMenB+OMV NZ.

MenABCWY: A number of different vaccine formulations were evaluated in MenABCWY Phase I and II clinical studies. The formulation with the same active ingredient composition as the rMenB+OMV NZ (*Bexsero*) and MenACWY (*Menveo*) vaccines was chosen as the final formulation of the investigational MenABCWY vaccine. Two doses administered 6 months apart (0,6-months) is considered the optimal dosing schedule, based on serogroup B immunogenicity results from MenABCWY Phase II clinical studies.

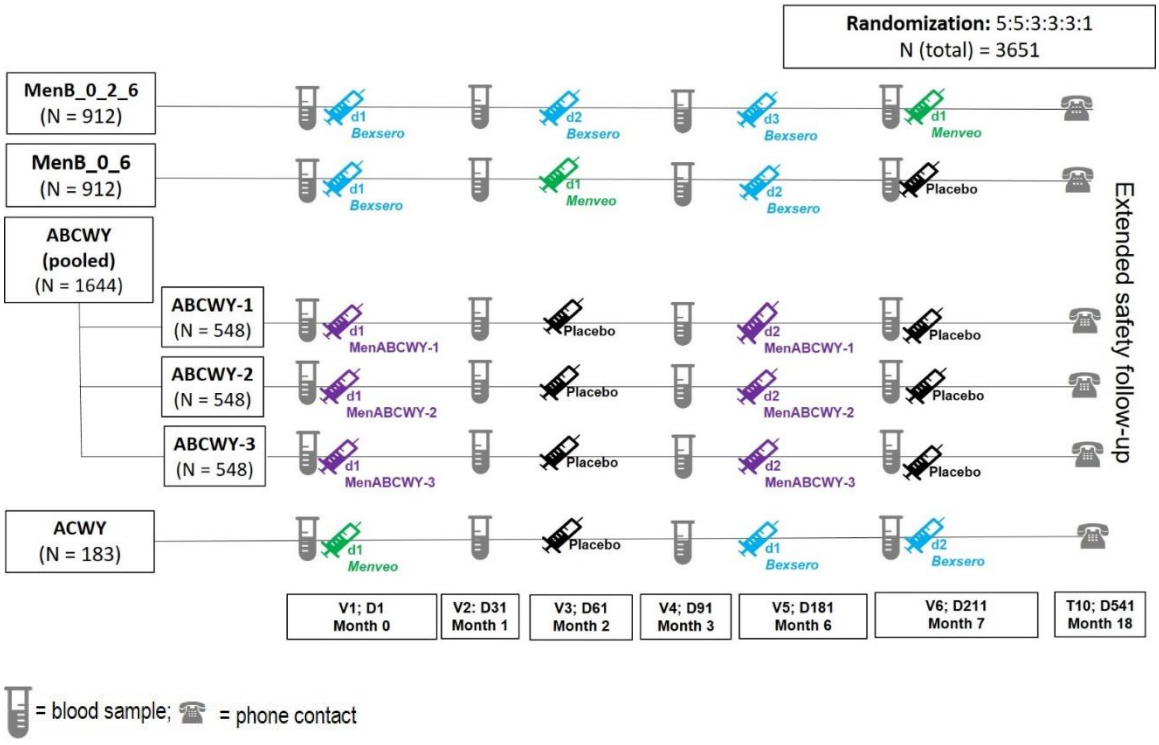
MenACWY: As a comparator for serogroup A, C, W, and Y vaccine effectiveness and immune responses, a single dose of MenACWY vaccine is administered to subjects in the ACWY group. To conform with the standard of care (also in alignment with current ACIP routine immunisation recommendations in US), subjects in the MenB_0_2_6 and MenB_0_6 groups will also receive a dose of MenACWY at Day 211 and Day 61, respectively.

3.1.1. Rationale for the use of placebo

For this study, a placebo (saline solution) will be administered as presented in Figure 1. A placebo is the only available option to minimize possible introduction of reporting bias in collecting information about AEs and to ensure the same number of vaccinations are administered to subjects assigned to either of the six study groups.

3.2. Overall design

Figure 1 Study design overview



N = number of subjects; d = dose; V = visit; D = day; T=Telephone call
Refer to Protocol Table 3 for details on all visits
Note: Home visits may be performed only by sites authorised (as per local regulations and sponsor agreement), with approved site level standard operating procedures (SOP) provided that the compliance with protocol procedures are ensured.

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the schedule of activities (Protocol Section 2), are essential and required for study conduct.

- Type of study: self-contained

- Experimental design: This is a phase III, randomised, controlled, observer-blind, multi-center study to evaluate effectiveness, immunogenicity and safety of rMenB+OMV NZ and MenABCWY vaccines. A total of 3651 healthy adolescents and young adults aged 10-25 years will be enrolled and randomised (5:5:3:3:3:1 ratio) to one of the six parallel study groups:

  – **MenB_0_2_6 group***: subjects will receive 3 doses of rMenB+OMV NZ at Day 1, Day 61 and Day 181 (0, 2 and 0,2,6-months schedule). These subjects will receive 1 dose of the MenACWY vaccine at Day 211**.

  – **MenB_0_6 group**: subjects will receive 2 doses of rMenB+OMV NZ at Day 1 and Day 181 and 1 dose of MenACWY vaccine at Day 61 (rMenB+OMV NZ, 0,6-months schedule). These subjects will receive 1 dose of placebo at Day 211**.

  – **ABCWY-1**: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 1 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211**.

  – **ABCWY-2**: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 2 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211**.

  – **ABCWY-3**: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 3 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211**.

  – **ACWY group**: subjects will receive 1 dose of MenACWY vaccine at Day 1, 1 dose of placebo at Day 61 and 2 doses of rMenB+OMV NZ at Day 181 and Day 211**.

  * MenB_0_2_6 group will also be evaluated for objectives pertaining to 0,2-months vaccination schedule.

  Note 1: A MenB lot will be used for the pre-filled syringe component of the MenABCWY vaccine.

  Note 2: The groups ABCWY-1, ABCWY-2, ABCWY-3 will be pooled into a single group, ABCWY (pooled lots) (except for analysis of lot to lot consistency).

  ** Note 3: In order to let the subjects in MenB_0_2_6 group receive a dose of MenACWY vaccine and for subjects in ACWY group to receive the second dose of rMenB+OMV NZ in line with the vaccine as standard of care (also in line with the Advisory Committee on Immunization Practices (ACIP) recommendations in the US [ACIP, 2011]), the subjects in these groups will receive a vaccination of MenACWY and rMenB+OMV NZ vaccines, respectively, on Day 211 (Visit 6) after completion of the post-vaccination 3 blood sampling. To maintain the blinding of the study, subjects in the rest of the groups (MenB_0_6, ABCWY-1, ABCWY-2 and ABCWY-3) will receive a dose of Placebo. All these vaccines/ product administered at Day 211 are not associated with any study objectives/ endpoints (Safety assessment

conducted after 1 dose of rMenB+OMV NZ in the ACWY group at Day 181 is to maintain the blind of the study).

- Duration of the study: The study duration is approximately 18 months for each subject.
- Primary completion Date (PCD): T10; Day 541.

Refer to Glossary of terms for the definition of PCD.

- End of Study (EoS): the date of release of the last testing results, to be achieved not later than 8 months after Last Subject Last Visit (LSLV) (LSLV = T10; Day 541). If the completion of testing occurs prior the completion of the LSLV the latter date defines the end of study visit.

Refer to Glossary of terms for the definition of EoS.

- Study groups:

Table 2 Study groups and treatment foreseen in the study

Study Groups	Number of subjects	Age (Min-Max)	Treatment name	Vaccine/Product name
MenB_0_2_6	912	10 – 25 y	*Bexsero* (Injection)	rMenB+OMV NZ
			Menveo (Injection)	MenACWY
MenB_0_6	912		*Bexsero* (Injection)	rMenB+OMV NZ
			Menveo (Injection)	MenACWY
			Placebo (Injection)	NaCl
ABCWY-1	548		MenABCWY (with Lot 1 of ACWY) (Injection)	MenABCWY-1
			Placebo (Injection)	NaCl
ABCWY-2	548		MenABCWY (with Lot 2 of ACWY) (Injection)	MenABCWY-2
			Placebo (Injection)	NaCl
ABCWY-3	548		MenABCWY (with Lot 3 of ACWY) (Injection)	MenABCWY-3
			Placebo (Injection)	NaCl
ACWY	183		*Menveo* (Injection)	MenACWY
			Placebo (Injection)	NaCl
			Bexsero (Injection)	rMenB+OMV NZ

Table 3 Overview of study design: Vaccination and Blood Draw Schedule

Visits **Study Day**	**Visit 1** **Day 1**	Visit 2 Day 31	**Visit** 3 **Day 61**	**Visit** 4 **Day 91**	**Visit** 5 **Day 181**	**Visit** 6 **Day 211**
Group **MenB_0_2_6** **N=912**	Pre-vacc Blood sample rMenB+OMV NZ	Post-vacc 1 Blood sample	rMenB+OMV NZ	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample MenACWY
Group **MenB_0_6** **N=912**	Pre-vacc Blood sample rMenB+OMV NZ	Post-vacc 1 Blood sample	MenACWY	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample Placebo
Group **ABCWY-1** **N=548**	Pre-vacc Blood sample MenABCWY-1	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-1	Post-vacc 3 Blood sample Placebo
Group **ABCWY-2** **N=548**	Pre-vacc Blood sample MenABCWY-2	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-2	Post-vacc 3 Blood sample Placebo
Group **ABCWY-3** **N=548**	Pre-vacc Blood sample MenABCWY-3	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-3	Post-vacc 3 Blood sample Placebo
Group **ACWY** **N=150**	Pre-vacc Blood sample MenACWY	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample rMenB+OMV NZ

N = number of subjects; Pre-vacc = pre-vaccination; Post-vacc = post-vaccination

- Treatment allocation: At Day 1, prior to the study vaccination, subjects will be randomised to 1 of the 6 study groups according to a 5:5:3:3:3:1 ratio.
- Blinding: Observer-blind. Kindly refer to Protocol Section 7.3 for details on blinding and unblinding procedures.
- Sampling schedule:
  - A total of 4 blood samples* will be collected from each subject at Day 1 (pre-vaccination blood sample; approximately 20 mL), at Day 31 (post-vaccination 1 blood sample; approximately 25 mL), at Day 91 (post-vaccination 2 blood sample; approximately 25 mL) and at Day 211 (post-vaccination-3 blood sample; approximately 25 mL).
  - Urine sampling: Urine samples for pregnancy testing will be collected from female subjects of child-bearing potential at Visit 1 (Day 1), Visit 3 (Day 61), Visit 5 (Day 181) and Visit 6 (Day 211) prior to the vaccination.

  * Insufficient blood volume may lead to test cancellation and jeopardise the statistical power. Hence, every effort must be done to collect blood volume as per protocol requirements.
- Data collection: standardised Electronic Case Report Form (eCRF). Solicited symptoms will be collected using a subject Diary (electronic Diary [eDiary]).
- Safety monitoring: Regular safety follow-up will be done through telephone calls (T). There will also be an extended safety follow-up (ESFU) phone call 12 months post-vaccination 3 (Day 181; Visit 5). This ESFU phone call will also mark the study conclusion. Refer to Protocol Table 3 and Protocol Section 8.5.3 for details on the safety follow-up.

3.3. Number of subjects

A total of 3651 subjects will be randomised in a ratio of 5:5:3:3:3:1; 912 each in MenB_0_2_6 and MenB_0_6 groups, 548 in each ABCWY groups and 183 in ACWY group. Assuming a 25% drop out rate, this should provide approximately 684 evaluable subjects in each of the MenB groups, 411 evaluable subjects in each of the ABCWY groups and 137 evaluable subjects in the ACWY group.

Refer to Protocol Section 10.1 for a detailed description of the criteria used in the determination of sample size.

Withdrawals will not be replaced.

3.4. Subject and study completion

A subject is considered to have completed the study, if the subject is available for the concluding contact (T10; Day 541) as described in the protocol.

Global completion of the study is required in order to provide enough subjects as defined in Protocol Section 10.1 Sample Size Determination.

4. ANALYSIS SETS

4.1. Definition

For purposes of analysis, the following analysis sets are defined:

4.1.1. Enrolled Set

Subject/ Subject for whom parent(s)/LAR's agreed to participate in a clinical study after completion of the informed consent process, who meet screening/eligibility criteria and randomized and/or received study intervention or undergone an invasive procedure.

4.1.2. Exposed Set

All subjects who received at least 1 dose of the study treatment. The allocation in a group is done in function of all administered treatments.

4.1.3. Full Analysis Set

All subjects who received at least 1 dose of the study treatment and have post-vaccination effectiveness or immunogenicity data.

4.1.4. Per Protocol Set

All subjects in the Full Analysis Set minus subjects with protocol deviations that lead to exclusion from the Per Protocol Set.

4.1.5. Solicited Safety Set

All subjects who received at least 1 dose of the study treatment (Exposed Set) who have solicited safety data beyond 30 minutes post vaccination.

4.1.6. Unsolicited Safety Set

All subjects who received at least 1 dose of the study treatment (Exposed Set) that report unsolicited AEs/report not having unsolicited AEs.

4.1.7. Overall Safety Set

All subjects that belong to the Unsolicited safety or/and to the Solicited safety set.

4.2. Criteria for eliminating data from Analysis Sets

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

4.2.1. Elimination from Exposed Set (ES)

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

4.2.2. Elimination from Per protocol Set (PPS)

4.2.2.1. Excluded subjects

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

Table 4 Elimination code and condition to exclude a subject from the PPS analysis

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
800	Fraudulent data	All	All
900	Invalid informed consent	All	All
1030	Study vaccine not administered at all	All	All
1050	Randomization failure	Visit 1, 3, 5	All
1060	Randomization code was broken	All	All
1070.1	Subjects got vaccinated with the correct vaccine but containing a lower volume	Visit 1, 3, 5	All
1070.2	Vaccination not according to protocol	Visit 1, 3, 5	All
1080	Vaccine temperature deviation	Visit 1, 3, 5	All
1090	Expired vaccine administered	Visit 1, 3, 5	All
1500.1	Other deviation from study procedures not able to classified under any other categories	All	All
1500.2	Any other GCP non-compliance not able to classified under any other categories	All	All
2010	Protocol violation (inclusion/exclusion criteria)	All	All
2040	Administration of any medication forbidden by the protocol	Visit 1, 3, 5	All
2050	Not withdrawn after developing withdrawal criteria other than prohibited concomitant vaccination/medication (medical condition forbidden)	All	All
2060	Concomitant infection related to the vaccine which may influence immune response (only meningococcal infection)	All	All
2080	Subjects did not comply with vaccination schedule	Visit 3, 5	All

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
2090	Subjects did not comply with blood sample schedule	Visit 2, 4, 6	All
2100	Serological results not available post-vaccination for all tests	Visit 2, 4, 6	All
2120	Obvious incoherence or abnormality or error in data related to testing	Visit 2, 4, 6	All
2130	Biological sample specimen procedures not compliant with protocol	Visit 2, 4, 6	All

4.2.3. Elimination from unsolicited and solicited safety set

4.2.3.1. Excluded subjects

4.2.3.1.1. Unsolicited safety set

Code 1030 (Study vaccine not administered at all), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1150 (no post-vaccination safety data) will be used for identifying subjects eliminated from the unsolicited safety set.

4.2.3.1.2. Solicited safety set

Code 1030 (Study vaccine not administered at all), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1160 (no post-vaccination solicited safety data) will be used for identifying subjects eliminated from the solicited safety set.

5. STATISTICAL ANALYSES

Standard data derivation rules and statistical methods are described in section 10.1 while the study specific data derivation rules and stat methods are described in section 9.

5.1. Disposition of subjects

5.1.1. Analysis of disposition of subjects planned in the protocol

Number of subjects enrolled, vaccinated subjects (at least 1 vaccination, full vaccination course), reason for early withdrawal, FAS, and PPS will be described by vaccine group.

5.1.2. Additional considerations

Not applicable

5.2. Demography and baseline characteristics analyses

5.2.1. Analysis of demography and baseline characteristics planned in the protocol

Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age, height, weight, and body mass index (BMI) at enrolment will be calculated overall and by vaccine group.

Distributions of subjects by sex, race, ethnic origin will be summarised overall and by vaccine group.

5.2.2. Additional considerations

A summary table of important protocol deviations related to COVID-19 will be provided. Also, a listing will be produced.

5.3. Primary effectiveness and immunogenicity

5.3.1. Analysis of primary effectiveness and immunogenicity planned in the protocol

Refer to Glossary of terms for definitions of test-based and responder-based vaccine effectiveness. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then all objectives for MenABCWY will be evaluated at 95% CI (Sections 5.3.1.7 through 5.3.1.11, ref Protocol Section 10.1).

5.3.1.1. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Analysis set: Per-protocol set (PPS) will be the primary analysis population

Statistical method: The VE is defined as 1- RR= (1- percentage of samples without bactericidal serum activity at 1:4 dilution in MenB group / percentage of samples without bactericidal serum activity at 1:4 dilution in the ACWY group) x100% and it will be analyzed using a generalised linear model with vaccine group, strain, and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) as independent variables. Furthermore, a repeated statement will be used to estimate the variance of the RR including correlation within subject's responses to different strains. If the statistical model does not converge due to (one of) the factor(s), a model without this/these factor(s) will be fitted instead. The response variable of the model will be the Bernoulli distributed outcome without bactericidal activity at a 1:4 dilution (i.e. response is 1 if titre < 4, and 0 if titre ≥ 4), at 1 month after the last vaccination (Month 7) in the MenB group and at Month 1 for the ACWY group. Each subject will contribute with approximately 35 measures to this analysis, each of the measures corresponding to the response variable to one of the 35 strains randomly assigned to be tested with the samples available for that specific subject.

In order to obtain the VE measure which is a measure based on the relative risk (RR), a generalised linear model will be used with the Binary distribution and link function log in order to compute the log RR and the corresponding 97.5% CI. The obtained values will be exponentiated to obtain the RR and the corresponding 97.5% CI. The VE will be computed as 100% x (1 – RR). Effectiveness of rMenB+OMV NZ (0,2,6-months schedule) will be demonstrated if the lower limit of the two-sided 97.5% CI for VE between MenB and the ACWY group is above 65%.

5.3.1.2. Effectiveness (Responder-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Analysis set: FAS will be the primary analysis population.

Statistical method: The percentage of responders (see definition in Glossary of terms) and the corresponding exact two-sided 97.5% CI based on Clopper-Pearson method will be calculated [Clopper, 1934].

The objective is to demonstrate that the lower limit of the 97.5% CI for the percentage of responders is higher than 65%.

5.3.1.3. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 5.3.1.1

5.3.1.4. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 5.3.1.2

5.3.1.5. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 5.3.1.1

5.3.1.6. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 5.3.1.2

5.3.1.7. Lot-to-lot consistency: MenABCWY - ACWY component

Analysis set: The analysis of lot-to-lot consistency will be based on the PPS.

Statistical method: For each of the three ABCWY lots (Lots 1, 2 and 3 of the MenACWY component of the ABCWY vaccine), GMTs and 97.5% CIs will be calculated by exponentiating (base 10) the least squares means and the lower and upper limits of the 97.5% CIs of the log transformed titres (base10) obtained from an Analysis of Variance

(ANOVA) with factors for vaccine lot and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)). Additionally, lot-to-lot GMT ratios will be computed for each pair of ABCWY lots. Ninety-seven point five percent (97.5%) CIs for the ratios of GMTs will be constructed by exponentiating the difference of the least square means of the log transformed titres and the lower and upper limits of the 97.5% CIs on the difference obtained from the ANOVA model above.

Lot-to-lot consistency criterion: The three ABCWY lots will be considered equivalent if for each of the 4 serogroups A, C, W and Y and each pair of vaccine lots, the two-sided 97.5% CI on the ratio of GMTs at 1 month after the last vaccination will be contained within the interval [0.5, 2.0].

If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.1.8. Immunological non-inferiority: MenABCWY vs. MenACWY

Analysis set: PPS restricted to subjects without previous ACWY vaccination will be the primary analysis population.

Statistical method: The percentage of subjects with 4-fold riseP*P in hSBA titres against MenACWY indicator strains A, C, W and Y and the corresponding exact two-sided 97.5% CIs based on Clopper-Pearson method will be calculated for the ABCWY (pooled lots) group and the ACWY group [Clopper, 1934]. The 97.5% CIs for the difference in percentages between ABCWY (pooled lots) and ACWY group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-Inferiority criterion: Non-inferiority of MenABCWY vaccine for the proportion of subjects with 4-fold rise will be demonstrated if the lower limit of the two-sided 97.5% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY (pooled) lots –ACWY) is above -10%.

* For the Men A, C, W, Y evaluation, the 4-fold rise is defined as:

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

Table 5 reads the LOD and LLOQ of MenACWY indicator strains used in the definition of 4-fold rise provided by the laboratory.

Table 5 LOD, LLOQ, and ULOQ of MenACWY indicator strains

Strain	LOD	LLOQ	ULOQ
Men A (3125)	CCI [redacted]		
Men C (C11)			
Men W (240070)			
Men Y (860800)			

If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.1.9. Vaccine effectiveness (Test-based): MenABCWY

See Section 5.3.1.1. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the VE for MenABCWY will be evaluated at 95% CI.

5.3.1.10. Effectiveness non-inferiority: MenABCWY vs. rMenB+OMV NZ

Analysis set: PPS will be the primary analysis population.

Statistical method: The percentage of samples with bactericidal activity measured by enc-hSBA at 1:4 dilution and the corresponding exact two-sided 97.5% CIs based on Clopper-Pearson method will be calculated for the ABCWY (pooled lots) group and the MenB group comparator that will be selected (ref: the footnote of Figure 2). The 97.5% CIs for the difference in percentages between ABCWY (pooled lots) and selected MenB group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-Inferiority criterion: Non-inferiority of MenABCWY vaccine for the percentage of samples with bactericidal activity measured by enc-hSBA at 1:4 dilution will be demonstrated if the lower limit of the two-sided 97.5% CI for the difference between the 2 groups (ABCWY (pooled) lots – MenB) is above -5%.

If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.1.11. Effectiveness (Responder-based): MenABCWY

See Section 5.3.1.2. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the effectiveness (responder-based) for MenABCWY will be evaluated at 95% CI.

5.3.2. Additional considerations

Analyses of the primary effectiveness and immunogenicity objectives will be repeated by age group (10-17 years of age and 18-25 years of age), race, sex, region (US/ ex-US), and subjects with and without a previous MenACWY vaccination (primed and unprimed).

5.3.2.1. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

The SAS code to analyse the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) objective is specified below. Treatment, region, age category, previous ACWY vaccination, and strains will be modelled as fixed effect. To account for a possible over-dispersion, the DSCALE option in the model statement will be evaluated first. The DSCALE will be kept in the model only if the F-statistics for the DSCALE parameter is significant ($p<0.05$). The following SAS code will be used for the VE calculation:

```
ods trace on;
ods output GEEEmpPEst = genmod_stats
CONVERGENCESTATUS = converge ;

PROC GENMOD data=dataset descending;
class trtgrp strain region agecat previousACWY subject_id ;
model outcome = trtgrp strain region agecat previousACWY / dist= bin
link= log DSCALE;
repeated subject = subject_id / type= CS withinsubject= strain;
estimate 'MenB026-ACWY' trtgrp 1 0 0 0 0 -1/ alpha=0.025 exp;

/*trtgrp R is MenB0,2,6 and trtgrp W is ACWY*/

run;

ods output close;

data genmod_stats;
set genmod_stats;
where parm = 'trtgrp' and level1 = '1';
rr = exp(estimate);
ub = exp(uppercl);
ve = (1 - rr)*100 ;
ve_ll = (1 - ub) * 100 ;
if ve_ll > 65 then success = 1 ;
else success = 0 ;
run;
```

where outcome represents the Bernoulli distributed outcome without bactericidal activity at a 1:4 dilution (i.e. response is 1 if titre < 4, and 0 if titre ≥ 4), one month after the 3rd vaccination in MenB 0,2,6 and one month after the MenACWY vaccination for the ACWY arm, trtgrp indicates the vaccine groups, strain is the serogroup B strain variable, region is either US or ex-US, agecat is the age at enrolment (10-17 YoA or 18-25 YoA), and previousACWY is previous ACWY vaccination (y/n) at enrolment.

rr is the relative risk (RR), which is obtained from the estimated parameters from PROC GENMOD. Vaccine effectiveness (VE) is then derived as (1-rr)x100%.

ub represents the upper bound of the 97.5% CI of the relative risk. ve_ll is the lower bound of the 97.5% CI for VE, if the value is greater than 65%, then the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) objective is successful.

5.3.2.2. Effectiveness (Responder-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Not applicable

5.3.2.3. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 5.3.2.1, with the difference in the treatment arm:

```
PROC GENMOD data=dataset descending;
class trtgrp strain region agecat previousACWY subject_id ;
model outcome = trtgrp strain region agecat previousACWY / dist= bin
link= log DSCALE ;
repeated subject = subject_id / type= CS withinsubject= strain ;
estimate 'MenB06-ACWY' trtgrp 0 1 0 0 0 -1/ alpha=0.025 exp;

/*trtgrp S is MenB0,6 and trtgrp W is ACWY*/

run;
```

5.3.2.4. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

Not applicable

5.3.2.5. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 5.3.2.1, with the difference the outcome data for group R is from one month after the 2nd vaccination instead of one month after the 3rd vaccination.

5.3.2.6. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

Not applicable

5.3.2.7. Lot-to-lot consistency: MenABCWY - ACWY component

Not applicable

5.3.2.8. Immunological non-inferiority: MenABCWY vs. MenACWY

As a sensitivity analysis, a parametric model will be run. A generalized linear model with factors for vaccine group and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA)) will be ran, with the Binary distribution and link function is identity, and outcome is 4-fold rise. If the lower limit of the two-sided 97.5% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY (pooled) lots –ACWY) coming from the model is above -10%, also the sensitivity analysis has demonstrated non-inferiority. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.2.9. Vaccine effectiveness (Test-based): MenABCWY

See Section 5.3.2.1, with the difference in the estimate statement:

```
PROC GENMOD data=dataset descending;
class trtgrp strain region agecat previousACWY subject_id ;
model outcome = trtgrp strain region agecat previousACWY / dist= bin
link= log DSCALE ;
repeated subject = subject_id / type= CS withinsubject= strain ;
estimate 'MenABCWY-ACWY' trtgrp 0 0 1 1 1 -3/ alpha=0.025 exp
divisor=3;

/*trtgrp T, U, and V are the ABCWY-1, ABCWY-2, and ABCWY-3 lots and
trtgrp W is ACWY*/
run;
```

5.3.2.10. Effectiveness non-inferiority: MenABCWY vs. rMenB+OMV NZ

As a sensitivity analysis, a parametric model will be run. A generalized linear model with factors for vaccine group and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) will be ran, with the Binary distribution and link function is identity, and outcome is bactericidal activity measured by enc-hSBA at 1:4 dilution. If the lower limit of the two-sided 97.5% CI for the difference in percentage of samples with bactericidal activity measured by enc-hSBA at 1:4 dilution between the 2 groups (ABCWY (pooled) lots –MenB) coming from the model is above -5%, also the sensitivity analysis has demonstrated non-inferiority. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

In addition to the comparison of MenABCWY vs the selected MenB schedule per Section 5.3.1.10, MenABCWY will be compared to the other MenB schedule/schedules, whichever is applicable in the same way as described in Section 5.3.1.10. If MenB 0,2 schedule is selected as comparator, in addition MenABCWY will be compared to Menb 0,6 and MenB 0,2,6 schedule. If MenB 0,6 schedule is selected as comparator, in addition MenABCWY will be compared to MenB 0,2,6 schedule. No success criterion is defined for these group comparisons.

5.3.2.11. Effectiveness (Responder-based): MenABCWY

Not applicable

5.4. Secondary effectiveness and immunogenicity

5.4.1. Analysis of secondary effectiveness and immunogenicity planned in the protocol

5.4.1.1. Immunological non-inferiority: MenABCWY vs. rMenB+OMV NZ

Analysis set: PPS will be the primary analysis population.

Statistical method: The percentages of subjects with 4-fold rise* in hSBA titres against N. meningitidis serogroup B indicator strains (M14459, 96217, M13520 and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively) at 1 month after the last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) and 1 month after the 3-dose vaccination series (Day 211, Month 7) in MenB_0_2_6 group or 2-dose vaccination series (Day 211, Month 7) in MenB_0_6 group or 2-dose vaccination series (Day 91, Month 3) in MenB_0_2_6 group and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated [Clopper, 1934]. The 95% CIs for the difference in percentages between ABCWY group (pooled lots) and MenB_0_2_6 group and MenB_0_6 group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-inferiority criterion: Non-inferiority of MenABCWY vaccine for the proportion of subjects with 4-fold rise will be demonstrated if the lower limit of the 2-sided 95% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY group (pooled lots) –selected MenB group) is above -10%.

* For the MenB evaluation, the 4-fold rise per each indicator strain is defined as:

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

‡ = post-2nd vaccination for 0,6 and 0,2 schedule and post-3rd vaccination for 0,2,6 schedule).

Table 6 reads the LOD and LLOQ of hSBA titres against N. meningitidis serogroup B indicator strains used in the definition of 4-fold rise provided by the laboratory.

Table 6 LOD and LLOQ of hSBA titres against N. meningitidis serogroup B indicator strains

Strain	LOD	LLOQ
NZ98-254	CCI [redacted]	
96217		
M14459		
M13520		

5.4.1.2. Effectiveness by each of the endemic US N. meningitidis serogroup B strains

Analysis set: FAS will be the primary analysis population. The ABCWY (pooled lots) group and the MenB group comparator that will be selected (ref: the footnote of Figure 2) will be used for the purpose of this analysis.

Statistical method: The VE per strain will be calculated as described in Section 5.3.1.1, using a generalised linear model with vaccine group, and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) as independent variables, and alpha=0.05 leading to 95% CI. In case for a strain 100% response will be observed in both vaccine groups, VE against these strain will be assessed by calculating 95% CI for relative risk from raw proportions, and VE=1-RR.

5.4.1.3. Distribution of percentages of serogroup B invasive disease strains killed

Analysis set: FAS will be the primary analysis population. The ABCWY (pooled lots) group and the MenB group comparator that will be selected (ref: the footnote of Figure 2) will be used for the purpose of this analysis.

Statistical method: Summary statistics of the percentage of serogroup B invasive disease strains killed within a subject using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series of rMenB+OMV NZ and MenABCWY vaccines.

Summary statistics and 95% CI for the mean percentage will be presented, as well as a Figure of the cumulative distribution function.

5.4.1.4. Immune response of MenABCWY, rMenB+OMV NZ and MenACWY

Analysis set: The analysis will be based on the FAS.

Statistical method: The hSBA titres at each time point for all groups (ABCWY group (pooled lots), MenB_0_2_6 and MenB_0_6 groups) will be logarithmically transformed (base10) to fulfil the normal distribution assumption. For each N. meningitidis serogroup A, C, W and Y and each B indicator strain (M14459, 96217, M13520 and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively), the GMTs and GMRs (post-vaccination/baseline) will be obtained from an Analysis of Variance (ANOVA) with factors for vaccine group, region (US/ex-US), age category (10-17 YoA/18-25 YoA), and previous MenACWY vaccination (y/n), and then exponentiating the log-transformed means and their 95% CIs. The ratio of GMTs and GMRs between two groups and the corresponding CI will be estimated additionally.

The total IgG (as measured by ECL) against serogroups A, C, W and Y at baseline (Day 1, Month 0) and

- at 1 month after the first (Day 31, Month 1) and the last vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and
- at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1),

will be analyzed in a comparable way as described above for hSBA titres. Since total IgG is measured as concentration instead of titer, the resulting geometric mean of the concentrations is abbreviated as GMC.

Table 7 LLOQ and ULOQ of total IgG (as measured by ECL) MenACWY indicator strains

Strain	LLOQ	ULOQ
Men A	CCI [redacted]	
Men C		
Men W		
Men Y		

For each N. meningitidis A, C, W and Y and for each (individual response) and all (composite response) serogroup B indicator strain (M14459, M13520, 96217 and NZ98/254) the percentages of subjects with hSBA titres ≥LLOQ and of subjects with 4-fold rise and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated for each study group at each timepoint not previously analyzed. Ninety-five percent (95%) CIs for the difference in percentages between ABCWY (pooled lots) on the one hand and MenB_0_2_6, MenB_0_6, and ACWY groups, respectively, on the other hand, will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

For each N. meningitidis serogroup A, C, W and Y, analyses of hSBA GMTs, percentages of subjects with hSBA titres ≥LLOQ and of subjects with 4-fold rise, will be repeated by subjects with and without a previous MenACWY vaccination (primed and unprimed). Similarly, analyses of GMCs of the total IgG (as measured by ECL) against serogroups A, C, W and Y will be repeated by subjects with and without a previous MenACWY vaccination (primed and unprimed).

5.4.1.5. Cohen kappa level of agreement

The human serum bactericidal assay (hSBA) and the endogenous complement human serum bactericidal assay (enc-hSBA) provide two different types of results for B strains; the hSBA gives a quantitative, continuous result (hSBA titer) while the enc-hSBA gives a qualitative, categorical result (with/without bactericidal activity).

To assess the agreement between hSBA and enc-hSBA, the Kappa statistics [Cohen, 1960] will be used and the hSBA results will be categorized as follows:

- The hSBA will be categorized as <LLOQ and ≥LLOQ (Ref. Table 6). Agreement will be assessed versus the positive and negative categories of the enc-hSBA at 1:4 dilution.

To evaluate the strength of the agreement, the following scale [Landis, 1977] will be used:

Table 8 Strength of agreement scale

Kappa	Strength of Agreement
< 0.00	Poor
0.00-0.20	Slight
0.21-0.40	Fair
0.41-0.60	Moderate
0.61-0.80	Substantial
0.81-1.00	Almost Perfect

A 95% Confidence Interval (CI) will be provided together with the point estimate of the Kappa for each of the above situations. The McNemar test will be also performed using the same categorizations of the hSBA results as described above. The aforementioned comparisons/tests will be all performed overall across vaccine groups, separately for each serogroup B test strain. The following SAS code will be used for the Kappa calculation and the McNemar test:

```
PROC FREQ data=dataset;
table assay1_res*assay2_res / agree;
run;
```

where assay1_res represents the enc-hSBA result, assay2_res represents the precategorized hSBA result.

5.4.2. Additional considerations

5.4.2.1. Immunological non-inferiority: MenABCWY vs. rMenB+OMV NZ

As a sensitivity analysis, a parametric model will be run. A generalized linear model with factors for vaccine group and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) will be ran, with the Binary distribution and link function is identity, and outcome is 4-fold rise. If the lower limit of the two-sided 95% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY (pooled) lots –MenB) coming from the model is above -10%, also the sensitivity analysis has demonstrated non-inferiority.

5.4.2.2. Effectiveness by each of the endemic US N. meningitidis serogroup B strains

The SAS code to analyse the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) by strain is specified below. Treatment, and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) will be modelled as fixed effect. To account for a possible over-dispersion, the DSCALE option in the model statement will be evaluated first. The DSCALE will be kept in the model only if the F-statistics for the DSCALE parameter is significant ($p<0.05$). The following SAS code will be used for the VE calculation:

```
ods trace on;
ods output  GEEEmpPEst = genmod_stats
CONVERGENCESTATUS = converge ;

PROC GENMOD data=dataset descending;
class trtgrp region agecat previousACWY;
by strain ;
model outcome = trtgrp region agecat previousACWY / dist= bin link= log
DSCALE alpha=0.05;
estimate 'MenB026-ACWY' trtgrp 1 0 0 0 0 -1/ alpha= 0.05 exp;

/*trtgrp R is MenB0,2,6 and trtgrp W is ACWY*/

run;

ods output close;

data genmod_stats;
set genmod_stats;
by strain ;
where parm = 'trtgrp' and level1 = '1';
rr = exp(estimate);
ub = exp(uppercl);
ve = (1 - rr)*100 ;
ve_ll = (1 - ub) * 100 ;
if ve_ll > 65 then success = 1 ;
else success = 0 ;
run;
```

where outcome represents the Bernoulli distributed outcome without bactericidal activity at a 1:4 dilution (i.e. response is 1 if titre < 4, and 0 if titre ≥ 4), one month after the 3rd vaccination in MenB0,2,6 and one month after the MenACWY vaccination for the ACWY arm, trtgrp indicates the vaccine groups, strain is the serogroup B strain variable, region is either US or ex-US, agecat is the age at enrolment (10-17 YoA or 18-25 YoA), and previousACWY is previous ACWY vaccination (y/n) at enrolment.

rr is the relative risk (RR), which is obtained from the estimated parameters from PROC GENMOD. Vaccine effectiveness (VE) is then derived as (1-rr)x100%.

ub represents the upper bound of the 95% CI of the relative risk. ve_ll is the lower bound of the 95% CI for VE, if the value is greater than 65%, then the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) objective is successful.

In summary in case of convergence issue the following hierarchical decision tree will be applied

- Binary model including region, agecat, and previousACWY
- Binary model, excluding region, agecat, and previousACWY
- Cochran-Mantel-Haenszel (CMH) method (if strain has 100% killed or 0% killed for ANY treatment)
- VE set to 0% (if strain has 100% killed for both treatment)

5.4.2.3. Distribution of percentages of serogroup B invasive disease strains killed

Not applicable

5.4.2.4. Immune response of MenABCWY, rMenB+OMV NZ and MenACWY

Not applicable

5.5. Safety and reactogenicity

5.5.1. Analysis of safety and reactogenicity planned in the protocol

Distribution of subjects by vaccinations will be summarised by vaccine group for the Enrolled Set. In case of vaccination error, subjects will be analyzed “as treated” (according to the vaccine the subject received).

Analysis sets: Solicited Safety Set (solicited local and systemic adverse events and other solicited adverse events), Unsolicited Safety Set (unsolicited adverse events), and Overall Safety Set.

Endpoint	Statistical Analysis Methods
Primary	**Endpoints description**: The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) adverse events during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. All solicited adverse events will be summarised according to defined severity grading scales, see protocol section 12.5.9.3. Frequencies and percentages of subjects experiencing each adverse event will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic adverse event overall and at each time point will also be presented. Post-vaccination solicited adverse events reported from Day 1 to Day 7 will be summarised for the intervals Day 1-3, Day 4-7, and Day 1-7 by maximal severity and by vaccine group, excluding the 30-minute measurement, which will be summarised separately. The severity of solicited local adverse events, including redness (erythema) at injection site, swelling of skin at injection site, and hardness of skin at injection site will be summarised according to categories based on linear measurement: None (1 to 24mm); Mild (25 to 50mm); Moderate (51 to 100mm); Severe (>100mm). Injection site tenderness and systemic reactions (except fever) occurring up to 7 days after each vaccination at Day 1, Day 61 and Day 181 will be summarised according to "mild", "moderate" or "severe". Each solicited local and systemic adverse event will also be further summarised as "none" versus "any" (for fever the latter will be ≥38.0 °C). Use of antipyretics and analgesics will be summarised by frequency by type of use (prophylactic versus treatment) and percentage of subjects reporting use. Body temperature will be summarised 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 temperatures ≥ 38.0 °C and temperatures ≥ 40.0 °C will also be presented.
	Endpoints description: The frequencies and percentages of subjects with any unsolicited ***AEs*** (including all SAEs), ***AEs*** leading to withdrawal and medically attended ***AEs*** during the 7 and the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. The frequencies and percentages of subjects with SAEs, ***AEs*** leading to withdrawal***, AESIs*** and medically attended ***AEs*** throughout the study period. This analysis applies to all adverse events occurring during the study, judged either as possibly related, or not related to vaccination by the investigator, recorded in AE CRF, with a start date on or after the date of first vaccination. AE starting prior to the first vaccination will only be listed. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class. All reported adverse events, as well as adverse events judged by the investigator as possibly related to study vaccine, will be summarised 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 adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted. Separate summaries will be produced for the following categories: • Serious adverse events. • Adverse events that are possibly related to vaccine. • Adverse events of special interest. • Adverse event leading to withdrawal. • Adverse events leading to a medically attended visit. Data listings of all adverse events will be provided by subject. In addition, adverse events in the categories above will be provided as listed data. Local and systemic AEs will be analyzed by point estimates with associated 95% CIs [Clopper, 1934].

5.5.2. Additional considerations

For analyses of the safety and reactogenicity endpoints, subjects will be analyzed "as treated" according to the actual vaccination a subject received.

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

Analyses of safety objectives will be repeated by age group (10-17 years of age and 18-25 years of age), race, sex, region (US/ ex-US), and with and without a previous MenACWY vaccination (primed and unprimed).

A Table and Listing of COVID-19 AE cases will be provided.

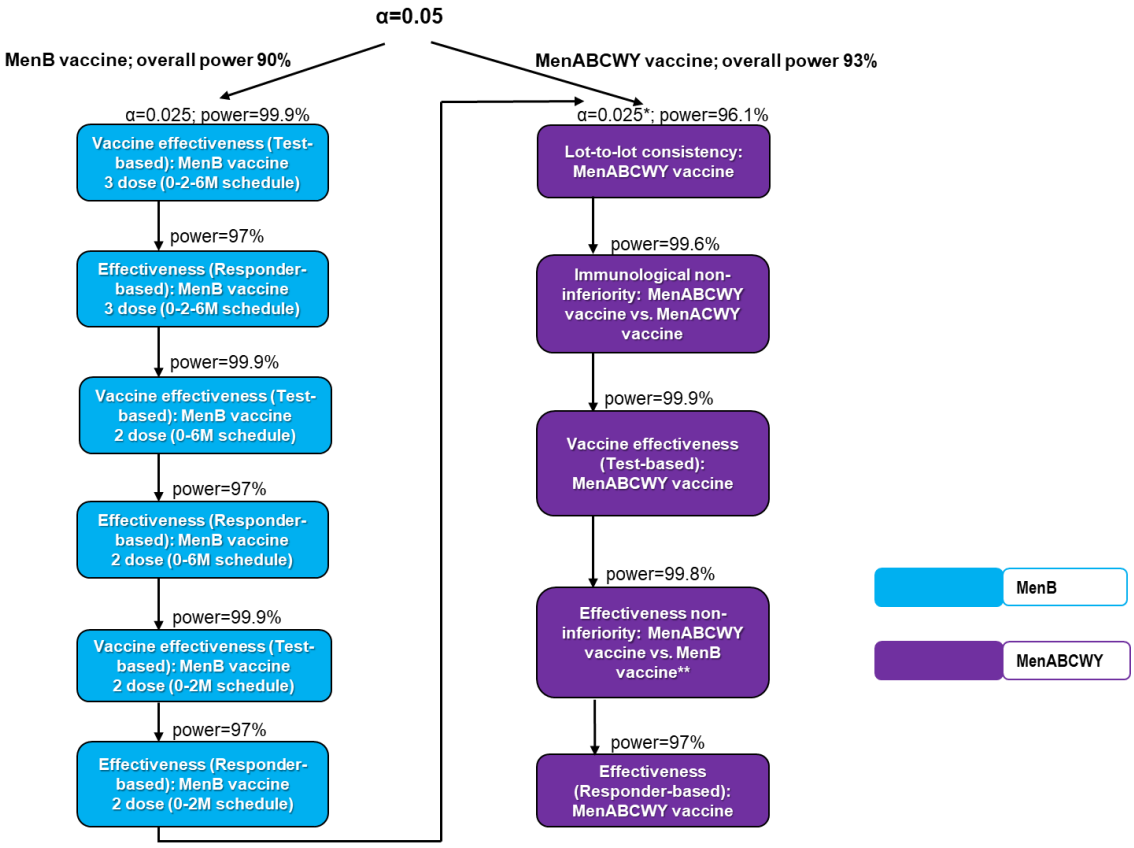
In case for a subject besides ediary data, also solicited reactions were recorded in the CRF, the CRF data will be mapped into the SDTM data with the ediary data (FA domain). For the analysis, the CRF data will be used in case of duplicate data.

6. ANALYSIS INTERPRETATION

Multiple objectives and endpoints require type I error control. Full alpha (0.05) is split equally (alpha=0.025) between rMenB+OMV NZ objectives and MenABCWY objectives. Furthermore, within rMenB+OMV NZ, as well as within MenABCWY, objectives are tested hierarchically. If the first null hypothesis is rejected, then the testing will continue with the second hypothesis at same alpha. Same for 3rd, 4th, and so forth. Whenever a null hypothesis is not rejected, then the testing will stop.

As the comparator for MenABCWY non inferiority objective for the B component will be the selected schedule of rMenB+OMV NZ as determined in this study, the objectives of rMenB+OMV NZ will be analysed first. Additionally, if all null hypotheses related to rMenB+OMV NZ objectives will be rejected, the alpha (alpha=0.025) will be propagated to the MenABCWY part, and hypotheses related to MenABCWY objectives will be tested at full alpha (alpha=0.05). See Figure 2 for an explanation of the hierarchical testing (top to bottom, the order indicated by the arrows).

Figure 2 Hierarchical testing of hypothesis



* Alpha split equally between rMenB+OMV NZ and MenABCWY vaccine objectives.
If all rMenB+OMV NZ objectives achieved, MenABCWY vaccine objectives will be tested at full alpha.
** If all objectives of rMenB+OMV NZ are met, the comparator will be the 0,2-months schedule. If the 0,2-months objective is not met, and the 0,6-months is met, then the 0,6-months schedule will be the comparator. If the 0,6-months is also not met, then the 0,2,6-months schedule will be the comparator.

Refer to Glossary of terms for definitions of test-based and responder-based vaccine effectiveness.

7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

The final study report will contain at least the final analyses of all primary and secondary endpoints.

7.2. Statistical considerations for interim analyses

No interim analysis is planned for this study

8. CHANGES FROM PLANNED ANALYSES

Not applicable

9. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

The following sections describe additional derivation rules and statistical methods which are not presented in section 10.1.

9.1. Data derivation

Not applicable

9.2. Statistical Method

Not applicable

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

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

10.1.1. Attributing events to vaccine doses

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

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

10.1.2. Handling of missing data

10.1.2.1. Dates

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

- A missing day will be replaced by 15

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

The following exceptions apply:

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

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

10.1.2.2. Laboratory data

Missing laboratory results (including immunological data) will not be replaced.

10.1.2.3. Daily recording of solicited adverse events

10.1.2.3.1. Studies with electronic diaries

For studies using electronic diaries for the collection of solicited adverse events, a solicited adverse events will be considered present only when a daily recording of grade 1 or more is present.

10.1.2.4. Unsolicited adverse events

Unsolicited adverse event summaries are including serious adverse events unless specified otherwise.

Missing severity, relationship with study vaccine, and outcome of unsolicited adverse events will not be replaced and will appear as 'UNKNOWN' in all statistical output.

10.1.3. Data derivation

10.1.3.1. Age at vaccination in days

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

Age = date of vaccination minus date of birth

10.1.3.2. Age at vaccination in months

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

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

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

10.1.3.3. Age at vaccination in years

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

DOB = 10SEP1983, Date of vaccination = 09SEP2018 -> Age = 34 years

DOB = 10SEP1983, Date of vaccination = 10SEP2018 -> Age = 35 years

10.1.3.4. Weight

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

Weight in kilograms = Weight in pounds / 2.2

10.1.3.5. Height

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

Height in centimeters = Height in inches x 2.54

10.1.3.6. Body mass index (BMI)

BMI will be calculated as follows:

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

10.1.3.7. Temperature

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

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

10.1.3.8. Numerical serology results

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

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

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

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

10.1.3.10. Onset day

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

10.1.3.11. Duration of events

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

10.1.3.12. Counting rules for combining solicited and unsolicited adverse events

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

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

10.1.3.13. Counting rules for occurrences of solicited adverse events

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

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with:

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

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

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

10.1.4.2. Differences in percentages

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

10.1.4.3. Demographic/baseline characteristics statistics

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

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

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

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

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

10.1.4.4. Serological summary statistics

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

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

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

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

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

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

10.1.5.2. Standardized asymptotic confidence intervals around differences in proportions

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

10.2. TFL TOC

The Tables Figures and Listings (TFL) Table of Contents (TOC) which itemizes the planned list of TFL and their associated lay-out is developed as a separate document.

10.3. Glossary of terms

End of Study (EoS) **(Synonym of End of Trial)**	For studies with collection of human biological samples and/or imaging data, the EoS is defined as Last subject last visit (T10). or Last testing results released of samples collected at Visit 6* * In this case EoS must be achieved no later than 8 months after LSLV.
Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.
Responder-based vaccine effectiveness:	The enc-hSBA methodology involves testing the serum samples from each individual subject against a subset of around 35 strains randomly chosen from the overall panel of 110 meningococcus B US strains. Responder-based vaccine effectiveness is assessed based on the percentage of subjects considered responders, i.e., subjects whose serum kills the majority (≥70% in this study) of the tested strains following vaccination.
Test-based vaccine effectiveness:	The enc-hSBA methodology involves testing the serum samples from each individual subject against a subset of around 35 strains randomly chosen from the overall panel of 110 meningococcus B US strains. Test-based vaccine effectiveness is assessed based on the overall percent of individual positive tests following vaccination and represents the reduction in risk compared to the placebo.

11. REFERENCES

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Landis J & Koch G, The Measurement of Observer Agreement for Categorical Data, *Biometrics,* 1977, **1**, p. 159.

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

Statistical Analysis Plan	
Detailed Title:	A phase III, randomized, controlled, observer-blind study to demonstrate effectiveness, immunogenicity and safety of GSK's meningococcal Group B and combined ABCWY vaccines when administered to healthy adolescents and young adults.
eTrack study number and Abbreviated Title	205416 [MENB REC 2ND GEN-038 (V72_72)]
Scope:	All data pertaining to the above study
Date of Statistical Analysis Plan	Amendment 8 Final: 30 Aug 2023

APP 9000058193 Statistical Analysis Plan Template V4 (Effective date: 3June2019)

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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
Eli Type	Internal database code for type of elimination code
ELISA	Enzyme-linked immunosorbent assay
EOS	End of Study
ES	Exposed Set
FAS	Full Analysis Set
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titre
GSK	GlaxoSmithKline
LL	Lower Limit of the confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
PCD	Primary completion Date
PPS	Per-Protocol Set
RR	Relative Risk
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
TFL	Tables Figures and Listings
TOC	Table of Contents

1. DOCUMENT HISTORY

Date	Description	Protocol Version
25 Jul 2019	First version	Amendment 1: 23 MAY 2019
15 Jun 2020	Amendment 1	Amendment 2: 18 MAR 2020
25 Mar 2022	Amendment 2	Amendment 4: 12 MAY 2021
25 Apr 2022	Amendment 3	Amendment 4: 12 MAY 2021
08 Sep 2022	Amendment 4	Amendment 4: 12 MAY 2021
12 Jan 2023	Amendment 5	Amendment 4: 12 MAY 2021
27 Feb 2023	Amendment 6	Amendment 4: 12 MAY 2021
14 Mar 2023	Amendment 7	Amendment 4: 12 MAY 2021
30 Aug 2023	Amendment 8	Amendment 4: 12 MAY 2021

2. OBJECTIVES/ENDPOINTS

Table 1 Study objectives and endpoints

Objectives	Endpoints
Primary	
Vaccine effectiveness (Test-based): rMenB+OMV NZ To demonstrate the effectiveness of the rMenB+OMV NZ vaccine against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity using enc-hSBA at 1 month after the 3-dose (0,2,6-months) and 2-dose (0,6-months; 0,2-months) vaccination series when compared to 1 month after the MenACWY vaccination. *Criterion* *Lower limit (LL) of the two-sided 97.5% confidence interval (CI) for vaccine effectiveness is above 65% against a randomly selected strain panel between the:* • *MenB_0_2_6 and ACWY groups (for 0,2,6-months schedule)* • *MenB_0_6 and ACWY groups (for 0,6-months schedule),* • *MenB_0_2_6 and ACWY groups (for 0,2-months schedule)*	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at 1 month after the: • 3-dose vaccination series in MenB_0_2_6 group (Day 211, Month 7) • 2-dose vaccination series in MenB_0_6 group (Day 211, Month 7), and • 2-dose vaccination series in MenB_0_2_6 group (Day 91, Month 3) • 1 month after the MenACWY vaccination in ACWY group (Day 31, Month 1).
Effectiveness (Responder-based): rMenB+OMV NZ To demonstrate the effectiveness of the rMenB+OMV NZ vaccine by assessing the percentages of subjects whose sera kill ≥70% of strains tested using enc-hSBA at 1 month after the 3-dose (0,2,6-months) and 2-dose (0,6-months; 0,2-months) vaccination series of the rMenB+OMV NZ. *Criterion:* *LL of the two-sided 97.5% CI for the percentages of subjects whose sera kill ≥70% of strains is above 65%, tested for:* • *MenB_0_2_6 group (for 0,2,6-months schedule)* • *MenB_0_6 group (for 0,6-months schedule),*	The percentages of subjects whose sera kill ≥70% of the strains tested using enc-hSBA, at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group), • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group)

Objectives	Endpoints
• *MenB_0_2_6 group (for 0,2-months schedule)*	
The 3 vaccine schedules will be tested for both, test-based and responder-based, in a hierarchical way (starting from 0-2-6, to 0-6 and 0-2). Refer to Protocol Section 10.1 for details on continuing the evaluation.	
Lot-to-lot consistency: MenABCWY vaccine To demonstrate lot-to-lot consistency of the immune responses of 3 lots of the MenACWY component of the MenABCWY vaccine, as measured by hSBA GMTs directed against serogroups A, C, W and Y at 1 month after last vaccination (0,6-months). *Criterion:* *The two-sided 97.5% CIs^ for the ratio of hSBA GMTs of antibodies against serogroups A, C, W and Y are within the [0.5;2.0] equivalence interval for each pair of lots*.	GMTs directed against serogroups A, C, W and Y for each lot (ABCWY-1 group, ABCWY-2 group, ABCWY-3 group) at 1 month after the last vaccination (Day 211, Month 7)
Immunological non-inferiority: MenABCWY vaccine vs. MenACWY vaccine To demonstrate the immunological non-inferiority of the MenABCWY vaccine compared to the MenACWY vaccine as measured by the percentages of subjects achieving a 4-fold rise in hSBA titres against *N. meningitidis* serogroups A, C, W and Y at 1 month after the last MenABCWY vaccination (0,6-months) and 1 month after the MenACWY vaccination. *Criterion:* *LL of the 2-sided 97.5% CI^ for the group difference in percentages of subjects achieving a 4-fold rise* in hSBA titres is above -10%.*	The percentages of subjects with 4-fold rise* in hSBA titres against *N. meningitidis* serogroups A, C, W and Y at 1 month after the: • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • 1 month after the MenACWY vaccination for the ACWY group (Day 31, Month 1) relative to baseline (Day 1, Month 0).
Vaccine effectiveness (Test-based): MenABCWY vaccine To demonstrate the effectiveness of the MenABCWY vaccine against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains as measured by enc-hSBA at 1 month after the last MenABCWY vaccination (0,6-months) when compared to 1 month after the MenACWY vaccination. *Criterion:* *LL of the two-sided 97.5% CI^ for vaccine effectiveness is above 65% against a randomly selected strain panel between the ABCWY group (pooled lots) and the ACWY group.*	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at 1 month after the: • last vaccination for the ABCWY group (pooled) (Day 211, Month 7), and • 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1).
Effectiveness non-inferiority: MenABCWY vaccine vs. rMenB+OMV NZ vaccine To demonstrate the non-inferiority of the effectiveness of the MenABCWY vaccine (0,6-months schedule) compared to the rMenB+OMV NZ vaccine (0,2,6-months or 0,6-months or 0,2-months)† in terms of percentage of samples with bactericidal serum activity using enc-hSBA against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains.	The percentages of samples with bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains at 1 month after the: • last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • 3-dose vaccination series of rMenB+OMV vaccine (Day 211, Month 7 in MenB_0_2_6 group) or 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) or 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group)†

Objectives	Endpoints
Criterion: *LL of the two-sided 97.5% CI^ for the difference in percentages of samples with bactericidal serum activity using enc-hSBA against a randomly selected panel of endemic US N. meningitidis serogroup B invasive disease strains is above -5% at 1 month after:* • *the last vaccination in ABCWY group (pooled lots) (for 0,6 months schedule), and* • *The last vaccination in MenB_0_2_6 group (for 0,2,6-months schedule) or the last vaccination in MenB_0_6 group (for 0,6-months schedule) or the second vaccination in MenB_0_2_6 group (for 0,2-months schedule*	
Effectiveness (Responder-based): MenABCWY vaccine To demonstrate the effectiveness of MenABCWY vaccine by assessing the percentages of subjects whose sera kill ≥70% of strains tested using enc-hSBA at 1 month after the last vaccination of MenABCWY (0,6-months). *Criterion:* *LL of the two-sided 97.5% CI^ for the percentages of subjects whose sera kill ≥70% of strains tested for MenABCWY is above 65%.*	The percentages of subjects whose sera kill ≥70% of the strains tested using enc-hSBA, at 1 month after the last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7).
Safety To evaluate the safety and reactogenicity of the MenB, MenABCWY, and the MenACWY vaccines	• The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [body temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) adverse events (AEs) during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. • The frequencies and percentages of subjects with any unsolicited AEs (including all SAEs, AEs leading to withdrawal, AESIs and medically attended AEs) during the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. • The percentages of subjects with SAEs, AEs leading to withdrawal, AESIs and medically attended AEs throughout the study period [Month 0 to Month 18].
Secondary	
To demonstrate the immunological non-inferiority of the MenABCWY vaccine compared to the rMenB+OMV NZ vaccine as measured by the percentages of subjects achieving a 4-fold rise in hSBA titres against *N. meningitidis* serogroup B indicator strains at 1 month after the last MenABCWY vaccination (0,6-months schedule) and 1 month after the rMenB+OMV NZ vaccination (0,2,6-months or 0,6-months or 0,2-months)†	The percentages of subjects with 4-fold rise** in hSBA titres against *N. meningitidis* serogroup B indicator strains at 1 month after the: • last MenABCWY vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • 3-dose vaccination series of rMenB+OMV vaccine(Day 211, Month 7 in MenB_0_2_6 group) or 2-dose vaccination series (Day 211, Month 7 in

Objectives	Endpoints
Criterion: *Non-inferiority will be demonstrated if the LL of the 2-sided 95% CI for the group difference in percentage of subjects achieving a 4-fold rise** in hSBA titres against N. meningitidis serogroup B indicator strains is above -10%.*	MenB_0_6 group) or 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group)† relative to baseline (Day 1, Month 0).
To assess the effectiveness of the rMenB+OMV NZ and MenABCWY vaccines against each of the randomly selected endemic US *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series when compared to 1 month after the MenACWY vaccination.	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group) • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • MenACWY vaccination (Day 31, Month 1 in ACWY group).
To describe the distribution of subjects by percentages of serogroup B invasive disease strains killed using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series of rMenB+OMV NZ and MenABCWY vaccines.	The percentages of serogroup B invasive disease strains killed using enc-hSBA in each subject at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7)
To assess the immune response to the rMenB+OMV NZ (0,2,6-months, 0,6-months and 0,2-months) and MenABCWY (0,6-months) vaccines against *N. meningitidis* serogroup B indicator strains at pre-vaccination (Day 1, Month 0) and at 1 month after the last MenABCWY vaccination and at 1 month after the second and third vaccination of rMenB+OMV NZ.	The immune response to the rMenB+OMV NZ and ABCWY vaccines will be evaluated by measuring bactericidal activity against *N. meningitidis* serogroup B indicator strains as following: *1. The percentages of subjects with hSBA titres ≥ lower limit of quantitation (LLOQ) for each (individual response) and all (composite response) serogroup B indicator strains at baseline (Day 1, Month 0) and at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *2. The percentages of subjects with 4-fold rise** in hSBA titres at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group)

Objectives	Endpoints
	• 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 90, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *relative to baseline (Day 1, Month 0).* *3. hSBA GMTs at baseline (Day 1, Month 0) and at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *4. hSBA GMRs at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *relative to the baseline (Day 1, Month 0).*
To assess the immune response to MenABCWY (0,6-months schedule) and MenACWY (single dose) vaccines against *N. meningitidis* serogroups A, C, W and Y, at pre-vaccination (Day 1, Month 0) and at 1 month after the first and the last MenABCWY vaccination and 1 month after the MenACWY vaccination.	*1. The percentage of subjects with hSBA titres ≥ LLOQ for serogroups A, C, W and Y at baseline (Day 1, Month 0) and:* • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1). *2. The percentage of subjects with 4-fold rise* in hSBA titres at 1 month after the:* • first vaccination (Day 31, Month 1) for the ABCWY group (pooled lots) compared to the MenACWY vaccination in the ACWY group (Day 31, Month 1) *relative to baseline (Day 1, Month 0).* *3. hSBA GMTs against N. meningitidis serogroups A, C, W and Y* at baseline (Day 1, Month 0) and: • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1). *4.hSBA GMRs against N. meningitidis serogroups A, C, W and Y at:* • 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7)

Objectives	Endpoints
	for the ABCWY group (pooled lots) as compared to baseline (Day 1, Month 0), and • 1 month after the single MenACWY vaccination in the ACWY group (Day 31, Month 1) as compared to baseline (Day 1, Month 0). *5.The total IgG as measured by ELISA GMCs against serogroups A, C, W and Y* at baseline (Day 1, Month 0) and*:* • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1).

Abbreviations: ELISA = enzyme-linked immunosorbent assay; Enc-hSBA = endogenous complement human serum bactericidal assay; GMC = geometric mean concentrations; GMT = geometric mean titre; GMR = geometric mean ratio; CI = confidence interval; hSBA = human serum bactericidal assay; LOD: limit of detection; LLOQ = lower limit of quantitation; LL = lower limit; AE = Adverse event; SAE = Serious adverse event; AESI = Adverse event of special interest

N.meningitidis serogroup B indicator strains = M14459, 96217, M13520 and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively.

Refer to Protocol Section 10 for details on evaluation of objectives and sample size justification. Refer to Glossary of terms for definitions of test-based and responder-based effectiveness

^ If the co-primary effectiveness objectives for rMenB+OMV NZ are met, then all objectives for MenABCWY will be evaluated at 95% CI. Refer to Protocol Section 10.1 for details

P† PIf all objectives of rMenB+OMV NZ are met, the comparator will be the 0,2-months schedule. If the 0,2-months objective is not met, and the 0,6-months is met, then the 0,6-months schedule will be the comparator. If the 0,6-months is also not met, then the 0,2,6-months schedule will be the comparator.

*For the Men A, C, W, Y evaluation, the 4-fold rise is defined as:

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

**For the MenB evaluation, the 4-fold rise per each indicator strain is defined as:

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

‡ = post-2nd vaccination for 0,6 and 0,2 schedule and post-3rd vaccination for 0,2,6 schedule.

3. STUDY DESIGN

3.1. Scientific rationale for study design

As the rMenB+OMV NZ licensure in the US was issued through accelerated approval, the FDA has requested to demonstrate the effectiveness of the vaccine against an extended panel of serogroup B meningococcal strains (MenB) as a post-marketing commitment in US adolescents and young adults, thus confirming that the vaccine can protect against diverse meningococcal B strains prevalent in the United States.

The availability of a pentavalent meningococcal vaccine in a single administration would however reduce the number of injections and could increase coverage for meningococcal disease caused by *N. meningitidis* serogroups A, B, C, W, and Y worldwide. GSK's investigational MenABCWY combination vaccine is intended to protect against 5 of the most prevalent serogroups of *Neisseria meningitidis* (A, B, C, W, Y) in humans.

Hence, along with the licensed MenB vaccine (*Bexsero*), this Phase III study will also assess the safety, effectiveness, and immunogenicity of the investigational MenABCWY vaccine.

Rationale for effectiveness assessment

As mentioned above, one of the primary purposes of this study is to evaluate the effectiveness of 2 or 3 doses of rMenB+OMV NZ and of 2 doses of the MenABCWY vaccines in healthy adolescents and young adults by measuring the bactericidal activity against 110 endemic US *N. meningitidis* serogroup B strains using an endogenous complement human Serum Bactericidal Assay (enc-hSBA). Sera from the ACWY group receiving the MenACWY vaccine will also be tested against serogroup B meningococcal strains by enc-hSBA as a control for test-based effectiveness assessment. The overall vaccine effectiveness (VE) against all 110 strains combined will be computed by means of a generalised linear model. For additional details see statistical analysis section of the Clinical Study Protocol (Protocol Section 10).

Rationale for lot-to-lot consistency assessment

MenABCWY is a reconstituted vaccine with the lyophilised 'ACWY component' and liquid rMenB+OMV NZ. The MenB component has the same formulation as the commercial *Bexsero*. To demonstrate that the lots of the investigational MenABCWY vaccine are adequately representative of the formulation intended for marketing, equivalence will be assessed for 3 different lots of the ACWY component of the ABCWY vaccine.

Rationale for non-inferiority assessment of MenABCWY vs MenACWY and rMenB+OMV NZ

The study aims to also demonstrate that the investigational combination MenABCWY vaccine is not inferior to a licensed MenACWY vaccine (*Menveo*) and a licensed MenB vaccine (*Bexsero*) which are part of the current standards of care in the US for prevention of invasive disease caused by *N. meningitidis* serogroups A, C, W, Y and by *N. meningitidis* serogroup B, respectively.

Rationale for blood volume collected:

In order to provide the necessary serum volume for the bactericidal assays (enc-hSBA and/ or hSBA(s)), 25 mL whole blood will be collected at Visit 2, Visit 4 and Visit 6. At pre-vaccination (Visit 1), 20 mL whole blood will be collected to provide the necessary serum volume for the hSBA.

Blood samples are taken from all subjects irrespective of the testing status in order to maintain the study blind. Refer to Protocol Section 8.4.2.1 for further details.

Rationale for the selected vaccination schedules

rMenB+OMV NZ: This study aims at demonstrating the VE of the rMenB+OMV NZ vaccine administered as 2-dose vaccine, either with a shorter interval (0,2-months) or a prolonged interval (0,6-months) between doses. A 3-dose schedule has been also added to better characterise the VE.

Note: The rMenB+OMV NZ in the ACWY group is administered in a 0,1-months schedule. This interval is within the recommendations in the summary of product characteristics of *Bexsero* and helps in maintaining the blind. No objectives are associated with this schedule of rMenB+OMV NZ.

MenABCWY: A number of different vaccine formulations were evaluated in MenABCWY Phase I and II clinical studies. The formulation with the same active ingredient composition as the rMenB+OMV NZ (*Bexsero*) and MenACWY (*Menveo*) vaccines was chosen as the final formulation of the investigational MenABCWY vaccine. Two doses administered 6 months apart (0,6-months) is considered the optimal dosing schedule, based on serogroup B immunogenicity results from MenABCWY Phase II clinical studies.

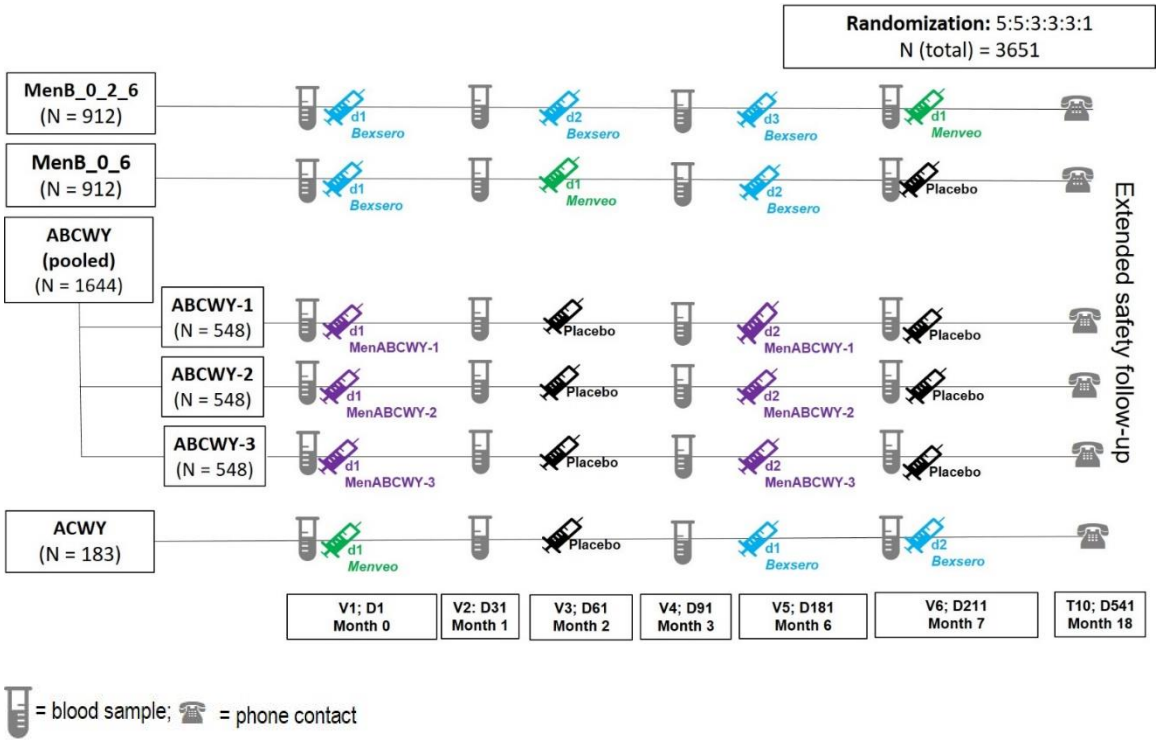
MenACWY: As a comparator for serogroup A, C, W, and Y vaccine effectiveness and immune responses, a single dose of MenACWY vaccine is administered to subjects in the ACWY group. To conform with the standard of care (also in alignment with current ACIP routine immunisation recommendations in US), subjects in the MenB_0_2_6 and MenB_0_6 groups will also receive a dose of MenACWY at Day 211 and Day 61, respectively.

3.1.1. Rationale for the use of placebo

For this study, a placebo (saline solution) will be administered as presented in Figure 1. A placebo is the only available option to minimize possible introduction of reporting bias in collecting information about AEs and to ensure the same number of vaccinations are administered to subjects assigned to either of the six study groups.

3.2. Overall design

Figure 1 Study design overview



N = number of subjects; d = dose; V = visit; D = day; T=Telephone call
Refer to Protocol Table 3 for details on all visits
Note: Home visits may be performed only by sites authorised (as per local regulations and sponsor agreement), with approved site level standard operating procedures (SOP) provided that the compliance with protocol procedures are ensured.

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the schedule of activities (Protocol Section 2), are essential and required for study conduct.

- Type of study: self-contained

- Experimental design: This is a phase III, randomised, controlled, observer-blind, multi-center study to evaluate effectiveness, immunogenicity and safety of rMenB+OMV NZ and MenABCWY vaccines. A total of 3651 healthy adolescents and young adults aged 10-25 years will be enrolled and randomised (5:5:3:3:3:1 ratio) to one of the six parallel study groups:

  – **MenB_0_2_6 group***: subjects will receive 3 doses of rMenB+OMV NZ at Day 1, Day 61 and Day 181 (0, 2 and 0,2,6-months schedule). These subjects will receive 1 dose of the MenACWY vaccine at Day 211**.

  – **MenB_0_6 group**: subjects will receive 2 doses of rMenB+OMV NZ at Day 1 and Day 181 and 1 dose of MenACWY vaccine at Day 61 (rMenB+OMV NZ, 0,6-months schedule). These subjects will receive 1 dose of placebo at Day 211**.

  – **ABCWY-1**: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 1 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211**.

  – **ABCWY-2**: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 2 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211**.

  – **ABCWY-3**: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 3 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211**.

  – **ACWY group**: subjects will receive 1 dose of MenACWY vaccine at Day 1, 1 dose of placebo at Day 61 and 2 doses of rMenB+OMV NZ at Day 181 and Day 211**.

  * MenB_0_2_6 group will also be evaluated for objectives pertaining to 0,2-months vaccination schedule.

  Note 1: A MenB lot will be used for the pre-filled syringe component of the MenABCWY vaccine.

  Note 2: The groups ABCWY-1, ABCWY-2, ABCWY-3 will be pooled into a single group, ABCWY (pooled lots) (except for analysis of lot to lot consistency).

  ** Note 3: In order to let the subjects in MenB_0_2_6 group receive a dose of MenACWY vaccine and for subjects in ACWY group to receive the second dose of rMenB+OMV NZ in line with the vaccine as standard of care (also in line with the Advisory Committee on Immunization Practices (ACIP) recommendations in the US [ACIP, 2011]), the subjects in these groups will receive a vaccination of MenACWY and rMenB+OMV NZ vaccines, respectively, on Day 211 (Visit 6) after completion of the post-vaccination 3 blood sampling. To maintain the blinding of the study, subjects in the rest of the groups (MenB_0_6, ABCWY-1, ABCWY-2 and ABCWY-3) will receive a dose of Placebo. All these vaccines/ product administered at Day 211 are not associated with any study objectives/ endpoints (Safety assessment

conducted after 1 dose of rMenB+OMV NZ in the ACWY group at Day 181 is to maintain the blind of the study).

- Duration of the study: The study duration is approximately 18 months for each subject.
- Primary completion Date (PCD): T10; Day 541.

Refer to Glossary of terms for the definition of PCD.

- End of Study (EoS): the date of release of the last testing results, to be achieved not later than 8 months after Last Subject Last Visit (LSLV) (LSLV = T10; Day 541). If the completion of testing occurs prior the completion of the LSLV the latter date defines the end of study visit.

Refer to Glossary of terms for the definition of EoS.

- Study groups:

Table 2 Study groups and treatment foreseen in the study

Study Groups	Number of subjects	Age (Min-Max)	Treatment name	Vaccine/Product name
MenB_0_2_6	912	10 – 25 y	*Bexsero* (Injection)	rMenB+OMV NZ
			Menveo (Injection)	MenACWY
MenB_0_6	912		*Bexsero* (Injection)	rMenB+OMV NZ
			Menveo (Injection)	MenACWY
			Placebo (Injection)	NaCl
ABCWY-1	548		MenABCWY (with Lot 1 of ACWY) (Injection)	MenABCWY-1
			Placebo (Injection)	NaCl
ABCWY-2	548		MenABCWY (with Lot 2 of ACWY) (Injection)	MenABCWY-2
			Placebo (Injection)	NaCl
ABCWY-3	548		MenABCWY (with Lot 3 of ACWY) (Injection)	MenABCWY-3
			Placebo (Injection)	NaCl
ACWY	183		*Menveo* (Injection)	MenACWY
			Placebo (Injection)	NaCl
			Bexsero (Injection)	rMenB+OMV NZ

Table 3 Overview of study design: Vaccination and Blood Draw Schedule

Visits **Study Day**	**Visit 1** **Day 1**	Visit 2 Day 31	**Visit** 3 **Day 61**	**Visit** 4 **Day 91**	**Visit** 5 **Day 181**	**Visit** 6 **Day 211**
Group **MenB_0_2_6** **N=912**	Pre-vacc Blood sample rMenB+OMV NZ	Post-vacc 1 Blood sample	rMenB+OMV NZ	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample MenACWY
Group **MenB_0_6** **N=912**	Pre-vacc Blood sample rMenB+OMV NZ	Post-vacc 1 Blood sample	MenACWY	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample Placebo
Group **ABCWY-1** **N=548**	Pre-vacc Blood sample MenABCWY-1	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-1	Post-vacc 3 Blood sample Placebo
Group **ABCWY-2** **N=548**	Pre-vacc Blood sample MenABCWY-2	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-2	Post-vacc 3 Blood sample Placebo
Group **ABCWY-3** **N=548**	Pre-vacc Blood sample MenABCWY-3	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-3	Post-vacc 3 Blood sample Placebo
Group **ACWY** **N=150**	Pre-vacc Blood sample MenACWY	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample rMenB+OMV NZ

N = number of subjects; Pre-vacc = pre-vaccination; Post-vacc = post-vaccination

- Treatment allocation: At Day 1, prior to the study vaccination, subjects will be randomised to 1 of the 6 study groups according to a 5:5:3:3:3:1 ratio.
- Blinding: Observer-blind. Kindly refer to Protocol Section 7.3 for details on blinding and unblinding procedures.
- Sampling schedule:
  - A total of 4 blood samples* will be collected from each subject at Day 1 (pre-vaccination blood sample; approximately 20 mL), at Day 31 (post-vaccination 1 blood sample; approximately 25 mL), at Day 91 (post-vaccination 2 blood sample; approximately 25 mL) and at Day 211 (post-vaccination-3 blood sample; approximately 25 mL).
  - Urine sampling: Urine samples for pregnancy testing will be collected from female subjects of child-bearing potential at Visit 1 (Day 1), Visit 3 (Day 61), Visit 5 (Day 181) and Visit 6 (Day 211) prior to the vaccination.

  * Insufficient blood volume may lead to test cancellation and jeopardise the statistical power. Hence, every effort must be done to collect blood volume as per protocol requirements.
- Data collection: standardised Electronic Case Report Form (eCRF). Solicited symptoms will be collected using a subject Diary (electronic Diary [eDiary]).
- Safety monitoring: Regular safety follow-up will be done through telephone calls (T). There will also be an extended safety follow-up (ESFU) phone call 12 months post-vaccination 3 (Day 181; Visit 5). This ESFU phone call will also mark the study conclusion. Refer to Protocol Table 3 and Protocol Section 8.5.3 for details on the safety follow-up.

3.3. Number of subjects

A total of 3651 subjects will be randomised in a ratio of 5:5:3:3:3:1; 912 each in MenB_0_2_6 and MenB_0_6 groups, 548 in each ABCWY groups and 183 in ACWY group. Assuming a 25% drop out rate, this should provide approximately 684 evaluable subjects in each of the MenB groups, 411 evaluable subjects in each of the ABCWY groups and 137 evaluable subjects in the ACWY group.

Refer to Protocol Section 10.1 for a detailed description of the criteria used in the determination of sample size.

Withdrawals will not be replaced.

3.4. Subject and study completion

A subject is considered to have completed the study, if the subject is available for the concluding contact (T10; Day 541) as described in the protocol.

Global completion of the study is required in order to provide enough subjects as defined in Protocol Section 10.1 Sample Size Determination.

4. ANALYSIS SETS

4.1. Definition

For purposes of analysis, the following analysis sets are defined:

4.1.1. Enrolled Set

Subject/ Subject for whom parent(s)/LAR's agreed to participate in a clinical study after completion of the informed consent process, who meet screening/eligibility criteria and randomized and/or received study intervention or undergone an invasive procedure.

4.1.2. Exposed Set

All subjects who received at least 1 dose of the study treatment. The allocation in a group is done in function of all administered treatments.

4.1.3. Full Analysis Set

All subjects who received at least 1 dose of the study treatment and have post-vaccination effectiveness or immunogenicity data.

4.1.4. Per Protocol Set

All subjects in the Full Analysis Set minus subjects with protocol deviations that lead to exclusion from the Per Protocol Set.

4.1.5. Solicited Safety Set

All subjects who received at least 1 dose of the study treatment (Exposed Set) who have solicited safety data beyond 30 minutes post vaccination.

4.1.6. Unsolicited Safety Set

All subjects who received at least 1 dose of the study treatment (Exposed Set) that report unsolicited AEs/report not having unsolicited AEs.

4.1.7. Overall Safety Set

All subjects that belong to the Unsolicited safety or/and to the Solicited safety set.

4.2. Criteria for eliminating data from Analysis Sets

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

4.2.1. Elimination from Exposed Set (ES)

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

4.2.2. Elimination from Per protocol Set (PPS)

4.2.2.1. Excluded subjects

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

Table 4 Elimination code and condition to exclude a subject from the PPS analysis

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
800	Fraudulent data	All	All
900	Invalid informed consent	All	All
1030	Study vaccine not administered at all	All	All
1050	Randomization failure	Visit 1, 3, 5	All
1060	Randomization code was broken	All	All
1070.1	Subjects got vaccinated with the correct vaccine but containing a lower volume	Visit 1, 3, 5	All
1070.2	Vaccination not according to protocol	Visit 1, 3, 5	All
1080	Vaccine temperature deviation	Visit 1, 3, 5	All
1090	Expired vaccine administered	Visit 1, 3, 5	All
1500.1	Other deviation from study procedures not able to classified under any other categories	All	All
1500.2	Any other GCP non-compliance not able to classified under any other categories	All	All
2010	Protocol violation (inclusion/exclusion criteria)	All	All
2040	Administration of any medication forbidden by the protocol	Visit 1, 3, 5	All
2050	Not withdrawn after developing withdrawal criteria other than prohibited concomitant vaccination/medication (medical condition forbidden)	All	All
2060	Concomitant infection related to the vaccine which may influence immune response (only meningococcal infection)	All	All
2080	Subjects did not comply with vaccination schedule	Visit 3, 5	All

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
2090	Subjects did not comply with blood sample schedule	Visit 2, 4, 6	All
2100	Serological results not available post-vaccination for all tests	Visit 2, 4, 6	All
2120	Obvious incoherence or abnormality or error in data related to testing	Visit 2, 4, 6	All
2130	Biological sample specimen procedures not compliant with protocol	Visit 2, 4, 6	All

4.2.3. Elimination from unsolicited and solicited safety set

4.2.3.1. Excluded subjects

4.2.3.1.1. Unsolicited safety set

Code 1030 (Study vaccine not administered at all), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1150 (no post-vaccination safety data) will be used for identifying subjects eliminated from the unsolicited safety set.

4.2.3.1.2. Solicited safety set

Code 1030 (Study vaccine not administered at all), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1160 (no post-vaccination solicited safety data) will be used for identifying subjects eliminated from the solicited safety set.

5. STATISTICAL ANALYSES

Standard data derivation rules and statistical methods are described in section 10.1 while the study specific data derivation rules and stat methods are described in section 9.

5.1. Disposition of subjects

5.1.1. Analysis of disposition of subjects planned in the protocol

Number of subjects enrolled, vaccinated subjects (at least 1 vaccination, full vaccination course), reason for early withdrawal, FAS, and PPS will be described by vaccine group.

5.1.2. Additional considerations

Not applicable

5.2. Demography and baseline characteristics analyses

5.2.1. Analysis of demography and baseline characteristics planned in the protocol

Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age, height, weight, and body mass index (BMI) at enrolment will be calculated overall and by vaccine group.

Distributions of subjects by sex, race, ethnic origin will be summarised overall and by vaccine group.

5.2.2. Additional considerations

A summary table of important protocol deviations related to COVID-19 will be provided. Also, a listing will be produced.

5.3. Primary effectiveness and immunogenicity

5.3.1. Analysis of primary effectiveness and immunogenicity planned in the protocol

Refer to Glossary of terms for definitions of test-based and responder-based vaccine effectiveness. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then all objectives for MenABCWY will be evaluated at 95% CI (Sections 5.3.1.7 through 5.3.1.11, ref Protocol Section 10.1).

5.3.1.1. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Analysis set: Per-protocol set (PPS) will be the primary analysis population

Statistical method: The VE is defined as 1- RR= (1- percentage of samples without bactericidal serum activity at 1:4 dilution in MenB group / percentage of samples without bactericidal serum activity at 1:4 dilution in the ACWY group) x100% and it will be analyzed using a generalised linear model with vaccine group, strain, and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) as independent variables. Furthermore, a repeated statement will be used to estimate the variance of the RR including correlation within subject's responses to different strains. If the statistical model does not converge due to (one of) the factor(s), a model without this/these factor(s) will be fitted instead. The response variable of the model will be the Bernoulli distributed outcome without bactericidal activity at a 1:4 dilution (i.e. response is 1 if titre < 4, and 0 if titre ≥ 4), at 1 month after the last vaccination (Month 7) in the MenB group and at Month 1 for the ACWY group. Each subject will contribute with approximately 35 measures to this analysis, each of the measures corresponding to the response variable to one of the 35 strains randomly assigned to be tested with the samples available for that specific subject.

In order to obtain the VE measure which is a measure based on the relative risk (RR), a generalised linear model will be used with the Binary distribution and link function log in order to compute the log RR and the corresponding 97.5% CI. The obtained values will be exponentiated to obtain the RR and the corresponding 97.5% CI. The VE will be computed as 100% x (1 – RR). Effectiveness of rMenB+OMV NZ (0,2,6-months schedule) will be demonstrated if the lower limit of the two-sided 97.5% CI for VE between MenB and the ACWY group is above 65%.

5.3.1.2. Effectiveness (Responder-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Analysis set: FAS will be the primary analysis population.

Statistical method: The percentage of responders (see definition in Glossary of terms) and the corresponding exact two-sided 97.5% CI based on Clopper-Pearson method will be calculated [Clopper, 1934].

The objective is to demonstrate that the lower limit of the 97.5% CI for the percentage of responders is higher than 65%.

5.3.1.3. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 5.3.1.1

5.3.1.4. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 5.3.1.2

5.3.1.5. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 5.3.1.1

5.3.1.6. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 5.3.1.2

5.3.1.7. Lot-to-lot consistency: MenABCWY - ACWY component

Analysis set: The analysis of lot-to-lot consistency will be based on the PPS.

Statistical method: For each of the three ABCWY lots (Lots 1, 2 and 3 of the MenACWY component of the ABCWY vaccine), GMTs and 97.5% CIs will be calculated by exponentiating (base 10) the least squares means and the lower and upper limits of the 97.5% CIs of the log transformed titres (base10) obtained from an Analysis of Variance

(ANOVA) with factors for vaccine lot and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)). Additionally, lot-to-lot GMT ratios will be computed for each pair of ABCWY lots. Ninety-seven point five percent (97.5%) CIs for the ratios of GMTs will be constructed by exponentiating the difference of the least square means of the log transformed titres and the lower and upper limits of the 97.5% CIs on the difference obtained from the ANOVA model above.

Lot-to-lot consistency criterion: The three ABCWY lots will be considered equivalent if for each of the 4 serogroups A, C, W and Y and each pair of vaccine lots, the two-sided 97.5% CI on the ratio of GMTs at 1 month after the last vaccination will be contained within the interval [0.5, 2.0].

If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.1.8. Immunological non-inferiority: MenABCWY vs. MenACWY

Analysis set: PPS restricted to subjects without previous ACWY vaccination will be the primary analysis population.

Statistical method: The percentage of subjects with 4-fold riseP*P in hSBA titres against MenACWY indicator strains A, C, W and Y and the corresponding exact two-sided 97.5% CIs based on Clopper-Pearson method will be calculated for the ABCWY (pooled lots) group and the ACWY group [Clopper, 1934]. The 97.5% CIs for the difference in percentages between ABCWY (pooled lots) and ACWY group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-Inferiority criterion: Non-inferiority of MenABCWY vaccine for the proportion of subjects with 4-fold rise will be demonstrated if the lower limit of the two-sided 97.5% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY (pooled) lots –ACWY) is above -10%.

* For the Men A, C, W, Y evaluation, the 4-fold rise is defined as:

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

Table 5 reads the LOD and LLOQ of MenACWY indicator strains used in the definition of 4-fold rise provided by the laboratory.

Table 5 LOD, LLOQ, and ULOQ of MenACWY indicator strains

Strain	LOD	LLOQ	ULOQ
Men A (3125)	CCI [redacted]		
Men C (C11)			
Men W (240070)			
Men Y (860800)			

If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.1.9. Vaccine effectiveness (Test-based): MenABCWY

See Section 5.3.1.1. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the VE for MenABCWY will be evaluated at 95% CI.

5.3.1.10. Effectiveness non-inferiority: MenABCWY vs. rMenB+OMV NZ

Analysis set: PPS will be the primary analysis population.

Statistical method: The percentage of samples with bactericidal activity measured by enc-hSBA at 1:4 dilution and the corresponding exact two-sided 97.5% CIs based on Clopper-Pearson method will be calculated for the ABCWY (pooled lots) group and the MenB group comparator that will be selected (ref: the footnote of Figure 2). The 97.5% CIs for the difference in percentages between ABCWY (pooled lots) and selected MenB group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-Inferiority criterion: Non-inferiority of MenABCWY vaccine for the percentage of samples with bactericidal activity measured by enc-hSBA at 1:4 dilution will be demonstrated if the lower limit of the two-sided 97.5% CI for the difference between the 2 groups (ABCWY (pooled) lots – MenB) is above -5%.

If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.1.11. Effectiveness (Responder-based): MenABCWY

See Section 5.3.1.2. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the effectiveness (responder-based) for MenABCWY will be evaluated at 95% CI.

5.3.2. Additional considerations

Analyses of the primary effectiveness and immunogenicity objectives will be repeated by age group (10-17 years of age and 18-25 years of age), race, sex, region (US/ ex-US), and subjects with and without a previous MenACWY vaccination (primed and unprimed).

5.3.2.1. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

The SAS code to analyse the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) objective is specified below. Treatment, region, age category, previous ACWY vaccination, and strains will be modelled as fixed effect. To account for a possible over-dispersion, the DSCALE option in the model statement will be evaluated first. The DSCALE will be kept in the model only if the F-statistics for the DSCALE parameter is significant ($p<0.05$). The following SAS code will be used for the VE calculation:

```
ods trace on;
ods output GEEEmpPEst = genmod_stats
CONVERGENCESTATUS = converge ;

PROC GENMOD data=dataset descending;
class trtgrp strain region agecat previousACWY subject_id ;
model outcome = trtgrp strain region agecat previousACWY / dist= bin
link= log DSCALE;
repeated subject = subject_id / type= CS withinsubject= strain;
estimate 'MenB026-ACWY' trtgrp 1 0 0 0 0 -1/ alpha=0.025 exp;

/*trtgrp R is MenB0,2,6 and trtgrp W is ACWY*/

run;

ods output close;

data genmod_stats;
set genmod_stats;
where parm = 'trtgrp' and level1 = '1';
rr = exp(estimate);
ub = exp(uppercl);
ve = (1 - rr)*100 ;
ve_ll = (1 - ub) * 100 ;
if ve_ll > 65 then success = 1 ;
else success = 0 ;
run;
```

where outcome represents the Bernoulli distributed outcome without bactericidal activity at a 1:4 dilution (i.e. response is 1 if titre < 4, and 0 if titre ≥ 4), one month after the 3rd vaccination in MenB 0,2,6 and one month after the MenACWY vaccination for the ACWY arm, trtgrp indicates the vaccine groups, strain is the serogroup B strain variable, region is either US or ex-US, agecat is the age at enrolment (10-17 YoA or 18-25 YoA), and previousACWY is previous ACWY vaccination (y/n) at enrolment.

rr is the relative risk (RR), which is obtained from the estimated parameters from PROC GENMOD. Vaccine effectiveness (VE) is then derived as (1-rr)x100%.

ub represents the upper bound of the 97.5% CI of the relative risk. ve_ll is the lower bound of the 97.5% CI for VE, if the value is greater than 65%, then the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) objective is successful.

5.3.2.2. Effectiveness (Responder-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Not applicable

5.3.2.3. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 5.3.2.1, with the difference in the treatment arm:

```
PROC GENMOD data=dataset descending;
class trtgrp strain region agecat previousACWY subject_id ;
model outcome = trtgrp strain region agecat previousACWY / dist= bin
link= log DSCALE ;
repeated subject = subject_id / type= CS withinsubject= strain ;
estimate 'MenB06-ACWY' trtgrp 0 1 0 0 0 -1/ alpha=0.025 exp;

/*trtgrp S is MenB0,6 and trtgrp W is ACWY*/

run;
```

5.3.2.4. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

Not applicable

5.3.2.5. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 5.3.2.1, with the difference the outcome data for group R is from one month after the 2nd vaccination instead of one month after the 3rd vaccination.

5.3.2.6. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

Not applicable

5.3.2.7. Lot-to-lot consistency: MenABCWY - ACWY component

Not applicable

5.3.2.8. Immunological non-inferiority: MenABCWY vs. MenACWY

As a sensitivity analysis, a parametric model will be run. A generalized linear model with factors for vaccine group and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA)) will be ran, with the Binary distribution and link function is identity, and outcome is 4-fold rise. If the lower limit of the two-sided 97.5% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY (pooled) lots –ACWY) coming from the model is above -10%, also the sensitivity analysis has demonstrated non-inferiority. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.2.9. Vaccine effectiveness (Test-based): MenABCWY

See Section 5.3.2.1, with the difference in the estimate statement:

```
PROC GENMOD data=dataset descending;
class trtgrp strain region agecat previousACWY subject_id ;
model outcome = trtgrp strain region agecat previousACWY / dist= bin
link= log DSCALE ;
repeated subject = subject_id / type= CS withinsubject= strain ;
estimate 'MenABCWY-ACWY' trtgrp 0 0 1 1 1 -3/ alpha=0.025 exp
divisor=3;

/*trtgrp T, U, and V are the ABCWY-1, ABCWY-2, and ABCWY-3 lots and
trtgrp W is ACWY*/
run;
```

5.3.2.10. Effectiveness non-inferiority: MenABCWY vs. rMenB+OMV NZ

As a sensitivity analysis, a parametric model will be run. A generalized linear model with factors for vaccine group and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) will be ran, with the Binary distribution and link function is identity, and outcome is bactericidal activity measured by enc-hSBA at 1:4 dilution. If the lower limit of the two-sided 97.5% CI for the difference in percentage of samples with bactericidal activity measured by enc-hSBA at 1:4 dilution between the 2 groups (ABCWY (pooled) lots –MenB) coming from the model is above -5%, also the sensitivity analysis has demonstrated non-inferiority. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

In addition to the comparison of MenABCWY vs the selected MenB schedule per Section 5.3.1.10, MenABCWY will be compared to the other MenB schedule/schedules, whichever is applicable in the same way as described in Section 5.3.1.10. If MenB 0,2 schedule is selected as comparator, in addition MenABCWY will be compared to Menb 0,6 and MenB 0,2,6 schedule. If MenB 0,6 schedule is selected as comparator, in addition MenABCWY will be compared to MenB 0,2,6 schedule. No success criterion is defined for these group comparisons.

5.3.2.11. Effectiveness (Responder-based): MenABCWY

Not applicable

5.4. Secondary effectiveness and immunogenicity

5.4.1. Analysis of secondary effectiveness and immunogenicity planned in the protocol

5.4.1.1. Immunological non-inferiority: MenABCWY vs. rMenB+OMV NZ

Analysis set: PPS will be the primary analysis population.

Statistical method: The percentages of subjects with 4-fold rise* in hSBA titres against N. meningitidis serogroup B indicator strains (M14459, 96217, M13520 and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively) at 1 month after the last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) and 1 month after the 3-dose vaccination series (Day 211, Month 7) in MenB_0_2_6 group or 2-dose vaccination series (Day 211, Month 7) in MenB_0_6 group or 2-dose vaccination series (Day 91, Month 3) in MenB_0_2_6 group and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated [Clopper, 1934]. The 95% CIs for the difference in percentages between ABCWY group (pooled lots) and MenB_0_2_6 group and MenB_0_6 group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-inferiority criterion: Non-inferiority of MenABCWY vaccine for the proportion of subjects with 4-fold rise will be demonstrated if the lower limit of the 2-sided 95% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY group (pooled lots) –selected MenB group) is above -10%.

* For the MenB evaluation, the 4-fold rise per each indicator strain is defined as:

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

‡ = post-2nd vaccination for 0,6 and 0,2 schedule and post-3rd vaccination for 0,2,6 schedule).

Table 6 reads the LOD and LLOQ of hSBA titres against N. meningitidis serogroup B indicator strains used in the definition of 4-fold rise provided by the laboratory.

Table 6 LOD and LLOQ of hSBA titres against N. meningitidis serogroup B indicator strains

Strain	LOD	LLOQ
NZ98-254	CCI [redacted]	
96217		
M14459		
M13520		

5.4.1.2. Effectiveness by each of the endemic US N. meningitidis serogroup B strains

Analysis set: FAS will be the primary analysis population. The ABCWY (pooled lots) group and the MenB group comparator that will be selected (ref: the footnote of Figure 2) will be used for the purpose of this analysis.

Statistical method: The VE per strain will be calculated as described in Section 5.3.1.1, using a generalised linear model with vaccine group, and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) as independent variables, and alpha=0.05 leading to 95% CI. In case for a strain 100% response will be observed in both vaccine groups, VE against these strain will be assessed by calculating 95% CI for relative risk from raw proportions, and VE=1-RR.

5.4.1.3. Distribution of percentages of serogroup B invasive disease strains killed

Analysis set: FAS will be the primary analysis population. The ABCWY (pooled lots) group and the MenB group comparator that will be selected (ref: the footnote of Figure 2) will be used for the purpose of this analysis.

Statistical method: Summary statistics of the percentage of serogroup B invasive disease strains killed within a subject using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series of rMenB+OMV NZ and MenABCWY vaccines.

Summary statistics and 95% CI for the mean percentage will be presented, as well as a Figure of the cumulative distribution function.

5.4.1.4. Immune response of MenABCWY, rMenB+OMV NZ and MenACWY

Analysis set: The analysis will be based on the FAS.

Statistical method: The hSBA titres at each time point for all groups (ABCWY group (pooled lots), MenB_0_2_6 and MenB_0_6 groups) will be logarithmically transformed (base10) to fulfil the normal distribution assumption. For each N. meningitidis serogroup A, C, W and Y and each B indicator strain (M14459, 96217, M13520 and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively), the GMTs and GMRs (post-vaccination/baseline) will be obtained from an Analysis of Variance (ANOVA) with factors for vaccine group, region (US/ex-US), age category (10-17 YoA/18-25 YoA), and previous MenACWY vaccination (y/n), and then exponentiating the log-transformed means and their 95% CIs. The ratio of GMTs and GMRs between two groups and the corresponding CI will be estimated additionally.

The total IgG (as measured by ECL) against serogroups A, C, W and Y at baseline (Day 1, Month 0) and

- at 1 month after the first (Day 31, Month 1) and the last vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and
- at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1),

will be analyzed in a comparable way as described above for hSBA titres. Since total IgG is measured as concentration instead of titer, the resulting geometric mean of the concentrations is abbreviated as GMC.

Table 7 LLOQ and ULOQ of total IgG (as measured by ECL) MenACWY indicator strains

Strain	LLOQ	ULOQ
Men A	CCI [redacted]	
Men C		
Men W		
Men Y		

For each N. meningitidis A, C, W and Y and for each (individual response) and all (composite response) serogroup B indicator strain (M14459, M13520, 96217 and NZ98/254) the percentages of subjects with hSBA titres ≥LLOQ and of subjects with 4-fold rise and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated for each study group at each timepoint not previously analyzed. Ninety-five percent (95%) CIs for the difference in percentages between ABCWY (pooled lots) on the one hand and MenB_0_2_6, MenB_0_6, and ACWY groups, respectively, on the other hand, will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

For each N. meningitidis serogroup A, C, W and Y, analyses of hSBA GMTs, percentages of subjects with hSBA titres ≥LLOQ and of subjects with 4-fold rise, will be repeated by subjects with and without a previous MenACWY vaccination (primed and unprimed). Similarly, analyses of GMCs of the total IgG (as measured by ECL) against serogroups A, C, W and Y will be repeated by subjects with and without a previous MenACWY vaccination (primed and unprimed).

5.4.1.5. Cohen kappa level of agreement

The human serum bactericidal assay (hSBA) and the endogenous complement human serum bactericidal assay (enc-hSBA) provide two different types of results for B strains; the hSBA gives a quantitative, continuous result (hSBA titer) while the enc-hSBA gives a qualitative, categorical result (with/without bactericidal activity).

To assess the agreement between hSBA and enc-hSBA, the Kappa statistics [Cohen, 1960] will be used and the hSBA results will be categorized as follows:

- The hSBA will be categorized as <LLOQ and ≥LLOQ (Ref. Table 6). Agreement will be assessed versus the positive and negative categories of the enc-hSBA at 1:4 dilution.

To evaluate the strength of the agreement, the following scale [Landis, 1977] will be used:

Table 8 Strength of agreement scale

Kappa	Strength of Agreement
< 0.00	Poor
0.00-0.20	Slight
0.21-0.40	Fair
0.41-0.60	Moderate
0.61-0.80	Substantial
0.81-1.00	Almost Perfect

A 95% Confidence Interval (CI) will be provided together with the point estimate of the Kappa for each of the above situations. The McNemar test will be also performed using the same categorizations of the hSBA results as described above. The aforementioned comparisons/tests will be all performed overall across vaccine groups, separately for each serogroup B test strain. The following SAS code will be used for the Kappa calculation and the McNemar test:

```
PROC FREQ data=dataset;
table assay1_res*assay2_res / agree;
run;
```

where assay1_res represents the enc-hSBA result, assay2_res represents the precategorized hSBA result.

5.4.2. Additional considerations

5.4.2.1. Immunological non-inferiority: MenABCWY vs. rMenB+OMV NZ

As a sensitivity analysis, a parametric model will be run. A generalized linear model with factors for vaccine group and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) will be ran, with the Binary distribution and link function is identity, and outcome is 4-fold rise. If the lower limit of the two-sided 95% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY (pooled) lots –MenB) coming from the model is above -10%, also the sensitivity analysis has demonstrated non-inferiority.

5.4.2.2. Effectiveness by each of the endemic US N. meningitidis serogroup B strains

The SAS code to analyse the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) by strain is specified below. Treatment, and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) will be modelled as fixed effect. To account for a possible over-dispersion, the DSCALE option in the model statement will be evaluated first. The DSCALE will be kept in the model only if the F-statistics for the DSCALE parameter is significant ($p<0.05$). The following SAS code will be used for the VE calculation:

```
ods trace on;
ods output  GEEEmpPEst = genmod_stats
CONVERGENCESTATUS = converge ;

PROC GENMOD data=dataset descending;
class trtgrp region agecat previousACWY;
by strain ;
model outcome = trtgrp region agecat previousACWY / dist= bin link= log
DSCALE alpha=0.05;
estimate 'MenB026-ACWY' trtgrp 1 0 0 0 0 -1/ alpha= 0.05 exp;

/*trtgrp R is MenB0,2,6 and trtgrp W is ACWY*/

run;

ods output close;

data genmod_stats;
set genmod_stats;
by strain ;
where parm = 'trtgrp' and level1 = '1';
rr = exp(estimate);
ub = exp(uppercl);
ve = (1 - rr)*100 ;
ve_ll = (1 - ub) * 100 ;
if ve_ll > 65 then success = 1 ;
else success = 0 ;
run;
```

where outcome represents the Bernoulli distributed outcome without bactericidal activity at a 1:4 dilution (i.e. response is 1 if titre < 4, and 0 if titre ≥ 4), one month after the 3rd vaccination in MenB0,2,6 and one month after the MenACWY vaccination for the ACWY arm, trtgrp indicates the vaccine groups, strain is the serogroup B strain variable, region is either US or ex-US, agecat is the age at enrolment (10-17 YoA or 18-25 YoA), and previousACWY is previous ACWY vaccination (y/n) at enrolment.

rr is the relative risk (RR), which is obtained from the estimated parameters from PROC GENMOD. Vaccine effectiveness (VE) is then derived as (1-rr)x100%.

ub represents the upper bound of the 95% CI of the relative risk. ve_ll is the lower bound of the 95% CI for VE, if the value is greater than 65%, then the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) objective is successful.

In summary in case of convergence issue the following hierarchical decision tree will be applied

- Binary model including region, agecat, and previousACWY
- Binary model, excluding region, agecat, and previousACWY
- Cochran-Mantel-Haenszel (CMH) method (if strain has 100% killed or 0% killed for ANY treatment)
- VE set to 0% (if strain has 100% killed for both treatment)

5.4.2.3. Distribution of percentages of serogroup B invasive disease strains killed

Not applicable

5.4.2.4. Immune response of MenABCWY, rMenB+OMV NZ and MenACWY

Not applicable

5.5. Safety and reactogenicity

5.5.1. Analysis of safety and reactogenicity planned in the protocol

Distribution of subjects by vaccinations will be summarised by vaccine group for the Enrolled Set. In case of vaccination error, subjects will be analyzed “as treated” (according to the vaccine the subject received).

Analysis sets: Solicited Safety Set (solicited local and systemic adverse events and other solicited adverse events), Unsolicited Safety Set (unsolicited adverse events), and Overall Safety Set.

Endpoint	Statistical Analysis Methods
Primary	**Endpoints description**: The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) adverse events during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. All solicited adverse events will be summarised according to defined severity grading scales, see protocol section 12.5.9.3. Frequencies and percentages of subjects experiencing each adverse event will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic adverse event overall and at each time point will also be presented. Post-vaccination solicited adverse events reported from Day 1 to Day 7 will be summarised for the intervals Day 1-3, Day 4-7, and Day 1-7 by maximal severity and by vaccine group, excluding the 30-minute measurement, which will be summarised separately. The severity of solicited local adverse events, including redness (erythema) at injection site, swelling of skin at injection site, and hardness of skin at injection site will be summarised according to categories based on linear measurement: None (1 to 24mm); Mild (25 to 50mm); Moderate (51 to 100mm); Severe (>100mm). Injection site tenderness and systemic reactions (except fever) occurring up to 7 days after each vaccination at Day 1, Day 61 and Day 181 will be summarised according to "mild", "moderate" or "severe". Each solicited local and systemic adverse event will also be further summarised as "none" versus "any" (for fever the latter will be ≥38.0 °C). Use of antipyretics and analgesics will be summarised by frequency by type of use (prophylactic versus treatment) and percentage of subjects reporting use. Body temperature will be summarised 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 temperatures ≥ 38.0 °C and temperatures ≥ 40.0 °C will also be presented.
	Endpoints description: The frequencies and percentages of subjects with any unsolicited ***AEs*** (including all SAEs), ***AEs*** leading to withdrawal and medically attended ***AEs*** during the 7 and the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. The frequencies and percentages of subjects with SAEs, ***AEs*** leading to withdrawal***, AESIs*** and medically attended ***AEs*** throughout the study period. This analysis applies to all adverse events occurring during the study, judged either as possibly related, or not related to vaccination by the investigator, recorded in AE CRF, with a start date on or after the date of first vaccination. AE starting prior to the first vaccination will only be listed. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class. All reported adverse events, as well as adverse events judged by the investigator as possibly related to study vaccine, will be summarised 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 adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted. Separate summaries will be produced for the following categories: • Serious adverse events. • Adverse events that are possibly related to vaccine. • Adverse events of special interest. • Adverse event leading to withdrawal. • Adverse events leading to a medically attended visit. Data listings of all adverse events will be provided by subject. In addition, adverse events in the categories above will be provided as listed data. Local and systemic AEs will be analyzed by point estimates with associated 95% CIs [Clopper, 1934].

5.5.2. Additional considerations

For analyses of the safety and reactogenicity endpoints, subjects will be analyzed "as treated" according to the actual vaccination a subject received.

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

Analyses of safety objectives will be repeated by age group (10-17 years of age and 18-25 years of age), race, sex, region (US/ ex-US), and with and without a previous MenACWY vaccination (primed and unprimed).

A Table and Listing of COVID-19 AE cases will be provided.

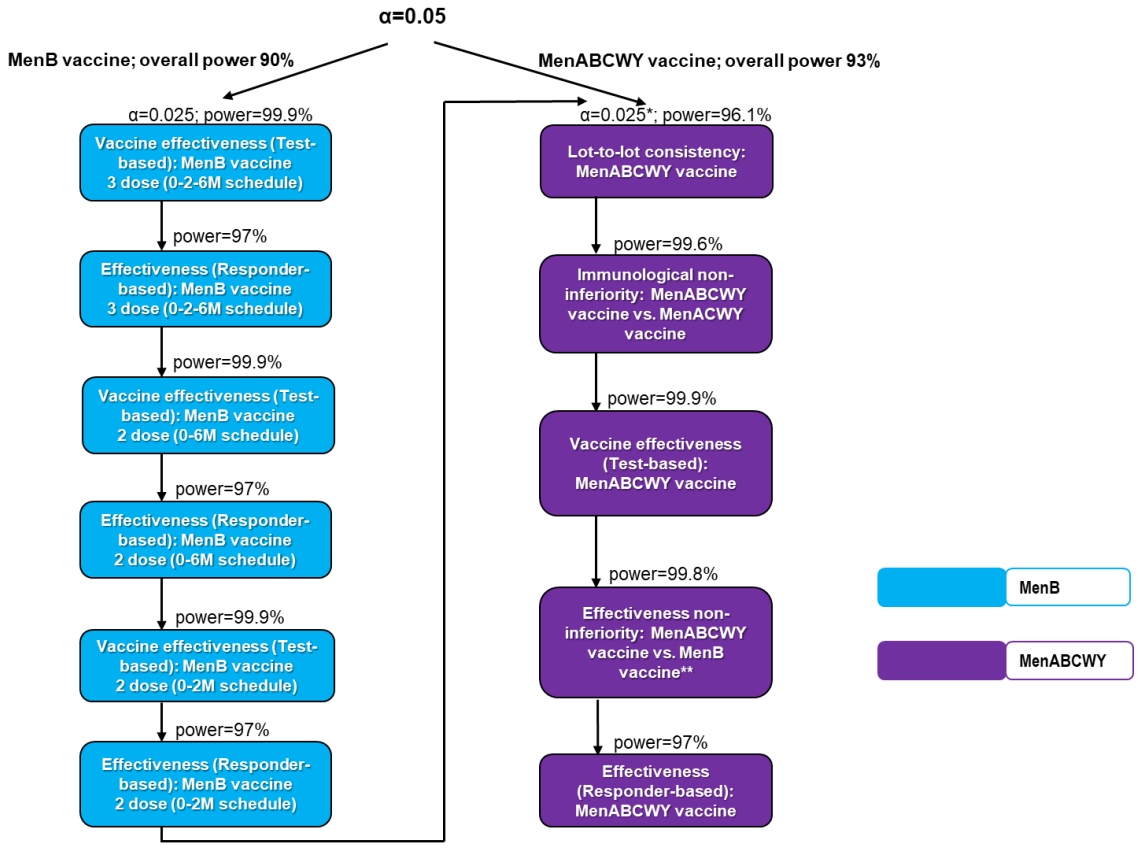
In case for a subject besides ediary data, also solicited reactions were recorded in the CRF, the CRF data will be mapped into the SDTM data with the ediary data (FA domain). For the analysis, the CRF data will be used in case of duplicate data.

6. ANALYSIS INTERPRETATION

Multiple objectives and endpoints require type I error control. Full alpha (0.05) is split equally (alpha=0.025) between rMenB+OMV NZ objectives and MenABCWY objectives. Furthermore, within rMenB+OMV NZ, as well as within MenABCWY, objectives are tested hierarchically. If the first null hypothesis is rejected, then the testing will continue with the second hypothesis at same alpha. Same for 3rd, 4th, and so forth. Whenever a null hypothesis is not rejected, then the testing will stop.

As the comparator for MenABCWY non inferiority objective for the B component will be the selected schedule of rMenB+OMV NZ as determined in this study, the objectives of rMenB+OMV NZ will be analysed first. Additionally, if all null hypotheses related to rMenB+OMV NZ objectives will be rejected, the alpha (alpha=0.025) will be propagated to the MenABCWY part, and hypotheses related to MenABCWY objectives will be tested at full alpha (alpha=0.05). See Figure 2 for an explanation of the hierarchical testing (top to bottom, the order indicated by the arrows).

Figure 2 Hierarchical testing of hypothesis



* Alpha split equally between rMenB+OMV NZ and MenABCWY vaccine objectives.
If all rMenB+OMV NZ objectives achieved, MenABCWY vaccine objectives will be tested at full alpha.
** If all objectives of rMenB+OMV NZ are met, the comparator will be the 0,2-months schedule. If the 0,2-months objective is not met, and the 0,6-months is met, then the 0,6-months schedule will be the comparator. If the 0,6-months is also not met, then the 0,2,6-months schedule will be the comparator.

Refer to Glossary of terms for definitions of test-based and responder-based vaccine effectiveness.

7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

The final study report will contain at least the final analyses of all primary and secondary endpoints.

7.2. Statistical considerations for interim analyses

No interim analysis is planned for this study

8. CHANGES FROM PLANNED ANALYSES

Not applicable

9. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

The following sections describe additional derivation rules and statistical methods which are not presented in section 10.1.

9.1. Data derivation

Not applicable

9.2. Statistical Method

Not applicable

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

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

10.1.1. Attributing events to vaccine doses

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

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

10.1.2. Handling of missing data

10.1.2.1. Dates

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

- A missing day will be replaced by 15

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

The following exceptions apply:

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

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

10.1.2.2. Laboratory data

Missing laboratory results (including immunological data) will not be replaced.

10.1.2.3. Daily recording of solicited adverse events

10.1.2.3.1. Studies with electronic diaries

For studies using electronic diaries for the collection of solicited adverse events, a solicited adverse events will be considered present only when a daily recording of grade 1 or more is present.

10.1.2.4. Unsolicited adverse events

Unsolicited adverse event summaries are including serious adverse events unless specified otherwise.

Missing severity, relationship with study vaccine, and outcome of unsolicited adverse events will not be replaced and will appear as 'UNKNOWN' in all statistical output.

10.1.3. Data derivation

10.1.3.1. Age at vaccination in days

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

Age = date of vaccination minus date of birth

10.1.3.2. Age at vaccination in months

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

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

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

10.1.3.3. Age at vaccination in years

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

DOB = 10SEP1983, Date of vaccination = 09SEP2018 -> Age = 34 years

DOB = 10SEP1983, Date of vaccination = 10SEP2018 -> Age = 35 years

10.1.3.4. Weight

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

Weight in kilograms = Weight in pounds / 2.2

10.1.3.5. Height

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

Height in centimeters = Height in inches x 2.54

10.1.3.6. Body mass index (BMI)

BMI will be calculated as follows:

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

10.1.3.7. Temperature

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

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

10.1.3.8. Numerical serology results

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

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

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

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

10.1.3.10. Onset day

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

10.1.3.11. Duration of events

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

10.1.3.12. Counting rules for combining solicited and unsolicited adverse events

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

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

10.1.3.13. Counting rules for occurrences of solicited adverse events

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

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with:

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

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

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

10.1.4.2. Differences in percentages

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

10.1.4.3. Demographic/baseline characteristics statistics

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

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

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

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

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

10.1.4.4. Serological summary statistics

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

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

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

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

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

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

10.1.5.2. Standardized asymptotic confidence intervals around differences in proportions

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

10.2. TFL TOC

The Tables Figures and Listings (TFL) Table of Contents (TOC) which itemizes the planned list of TFL and their associated lay-out is developed as a separate document.

10.3. Glossary of terms

End of Study (EoS) **(Synonym of End of Trial)**	For studies with collection of human biological samples and/or imaging data, the EoS is defined as Last subject last visit (T10). or Last testing results released of samples collected at Visit 6* * In this case EoS must be achieved no later than 8 months after LSLV.
Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.
Responder-based vaccine effectiveness:	The enc-hSBA methodology involves testing the serum samples from each individual subject against a subset of around 35 strains randomly chosen from the overall panel of 110 meningococcus B US strains. Responder-based vaccine effectiveness is assessed based on the percentage of subjects considered responders, i.e., subjects whose serum kills the majority (≥70% in this study) of the tested strains following vaccination.
Test-based vaccine effectiveness:	The enc-hSBA methodology involves testing the serum samples from each individual subject against a subset of around 35 strains randomly chosen from the overall panel of 110 meningococcus B US strains. Test-based vaccine effectiveness is assessed based on the overall percent of individual positive tests following vaccination and represents the reduction in risk compared to the placebo.

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

Statistical Analysis Plan	
Detailed Title:	A phase III, randomized, controlled, observer-blind study to demonstrate effectiveness, immunogenicity and safety of GSK's meningococcal Group B and combined ABCWY vaccines when administered to healthy adolescents and young adults.
eTrack study number and Abbreviated Title	205416 [MENB REC 2ND GEN-038 (V72_72)]
Scope:	All data pertaining to the above study
Date of Statistical Analysis Plan	Amendment 7 Final: 14 Mar 2023

APP 9000058193 Statistical Analysis Plan Template V4 (Effective date: 3June2019)

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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
Eli Type	Internal database code for type of elimination code
ELISA	Enzyme-linked immunosorbent assay
EOS	End of Study
ES	Exposed Set
FAS	Full Analysis Set
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titre
GSK	GlaxoSmithKline
LL	Lower Limit of the confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
PCD	Primary completion Date
PPS	Per-Protocol Set
RR	Relative Risk
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
TFL	Tables Figures and Listings
TOC	Table of Contents

1. DOCUMENT HISTORY

Date	Description	Protocol Version
25 Jul 2019	First version	Amendment 1: 23 MAY 2019
15 Jun 2020	Amendment 1	Amendment 2: 18 MAR 2020
25 Mar 2022	Amendment 2	Amendment 4: 12 MAY 2021
25 Apr 2022	Amendment 3	Amendment 4: 12 MAY 2021
08 Sep 2022	Amendment 4	Amendment 4: 12 MAY 2021
12 Jan 2023	Amendment 5	Amendment 4: 12 MAY 2021
27 Feb 2023	Amendment 6	Amendment 4: 12 MAY 2021
14 Mar 2023	Amendment 7	Amendment 4: 12 MAY 2021

2. OBJECTIVES/ENDPOINTS

Table 1 Study objectives and endpoints

Objectives	Endpoints
Primary	
Vaccine effectiveness (Test-based): rMenB+OMV NZ To demonstrate the effectiveness of the rMenB+OMV NZ vaccine against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity using enc-hSBA at 1 month after the 3-dose (0,2,6-months) and 2-dose (0,6-months; 0,2-months) vaccination series when compared to 1 month after the MenACWY vaccination. *Criterion* *Lower limit (LL) of the two-sided 97.5% confidence interval (CI) for vaccine effectiveness is above 65% against a randomly selected strain panel between the:* • *MenB_0_2_6 and ACWY groups (for 0,2,6-months schedule)* • *MenB_0_6 and ACWY groups (for 0,6-months schedule),* • *MenB_0_2_6 and ACWY groups (for 0,2-months schedule)*	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at 1 month after the: • 3-dose vaccination series in MenB_0_2_6 group (Day 211, Month 7) • 2-dose vaccination series in MenB_0_6 group (Day 211, Month 7), and • 2-dose vaccination series in MenB_0_2_6 group (Day 91, Month 3) • 1 month after the MenACWY vaccination in ACWY group (Day 31, Month 1).
Effectiveness (Responder-based): rMenB+OMV NZ To demonstrate the effectiveness of the rMenB+OMV NZ vaccine by assessing the percentages of subjects whose sera kill ≥70% of strains tested using enc-hSBA at 1 month after the 3-dose (0,2,6-months) and 2-dose (0,6-months; 0,2-months) vaccination series of the rMenB+OMV NZ. *Criterion:* *LL of the two-sided 97.5% CI for the percentages of subjects whose sera kill ≥70% of strains is above 65%, tested for:* • *MenB_0_2_6 group (for 0,2,6-months schedule)* • *MenB_0_6 group (for 0,6-months schedule),* • *MenB_0_2_6 group (for 0,2-months schedule)*	The percentages of subjects whose sera kill ≥70% of the strains tested using enc-hSBA, at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group), • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group)

Objectives	Endpoints
The 3 vaccine schedules will be tested for both, test-based and responder-based, in a hierarchical way (starting from 0-2-6, to 0-6 and 0-2). Refer to Protocol Section 10.1 for details on continuing the evaluation.	
Lot-to-lot consistency: MenABCWY vaccine To demonstrate lot-to-lot consistency of the immune responses of 3 lots of the MenACWY component of the MenABCWY vaccine, as measured by hSBA GMTs directed against serogroups A, C, W and Y at 1 month after last vaccination (0,6-months). *Criterion:* *The two-sided 97.5% CIs^ for the ratio of hSBA GMTs of antibodies against serogroups A, C, W and Y are within the [0.5;2.0] equivalence interval for each pair of lots*.	GMTs directed against serogroups A, C, W and Y for each lot (ABCWY-1 group, ABCWY-2 group, ABCWY-3 group) at 1 month after the last vaccination (Day 211, Month 7)
Immunological non-inferiority: MenABCWY vaccine vs. MenACWY vaccine To demonstrate the immunological non-inferiority of the MenABCWY vaccine compared to the MenACWY vaccine as measured by the percentages of subjects achieving a 4-fold rise in hSBA titres against *N. meningitidis* serogroups A, C, W and Y at 1 month after the last MenABCWY vaccination (0,6-months) and 1 month after the MenACWY vaccination. *Criterion:* *LL of the 2-sided 97.5% CI^ for the group difference in percentages of subjects achieving a 4-fold rise* in hSBA titres is above -10%.*	The percentages of subjects with 4-fold rise* in hSBA titres against *N. meningitidis* serogroups A, C, W and Y at 1 month after the: • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • 1 month after the MenACWY vaccination for the ACWY group (Day 31, Month 1) relative to baseline (Day 1, Month 0).
Vaccine effectiveness (Test-based): MenABCWY vaccine To demonstrate the effectiveness of the MenABCWY vaccine against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains as measured by enc-hSBA at 1 month after the last MenABCWY vaccination (0,6-months) when compared to 1 month after the MenACWY vaccination. *Criterion:* *LL of the two-sided 97.5% CI^ for vaccine effectiveness is above 65% against a randomly selected strain panel between the ABCWY group (pooled lots) and the ACWY group.*	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at 1 month after the: • last vaccination for the ABCWY group (pooled) (Day 211, Month 7), and • 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1).
Effectiveness non-inferiority: MenABCWY vaccine vs. rMenB+OMV NZ vaccine To demonstrate the non-inferiority of the effectiveness of the MenABCWY vaccine (0,6-months schedule) compared to the rMenB+OMV NZ vaccine (0,2,6-months or 0,6-months or 0,2-months)† in terms of percentage of samples with bactericidal serum activity using enc-hSBA against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains.	The percentages of samples with bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains at 1 month after the: • last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • 3-dose vaccination series of rMenB+OMV vaccine (Day 211, Month 7 in MenB_0_2_6 group) or 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) or 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group)†

Objectives	Endpoints
Criterion: *LL of the two-sided 97.5% CI^ for the difference in percentages of samples with bactericidal serum activity using enc-hSBA against a randomly selected panel of endemic US N. meningitidis serogroup B invasive disease strains is above -5% at 1 month after:* • *the last vaccination in ABCWY group (pooled lots) (for 0,6 months schedule), and* • *The last vaccination in MenB_0_2_6 group (for 0,2,6-months schedule) or the last vaccination in MenB_0_6 group (for 0,6-months schedule) or the second vaccination in MenB_0_2_6 group (for 0,2-months schedule*	
Effectiveness (Responder-based): MenABCWY vaccine To demonstrate the effectiveness of MenABCWY vaccine by assessing the percentages of subjects whose sera kill ≥70% of strains tested using enc-hSBA at 1 month after the last vaccination of MenABCWY (0,6-months). *Criterion:* *LL of the two-sided 97.5% CI^ for the percentages of subjects whose sera kill ≥70% of strains tested for MenABCWY is above 65%.*	The percentages of subjects whose sera kill ≥70% of the strains tested using enc-hSBA, at 1 month after the last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7).
Safety To evaluate the safety and reactogenicity of the MenB, MenABCWY, and the MenACWY vaccines	• The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [body temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) adverse events (AEs) during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. • The frequencies and percentages of subjects with any unsolicited AEs (including all SAEs, AEs leading to withdrawal, AESIs and medically attended AEs) during the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. • The percentages of subjects with SAEs, AEs leading to withdrawal, AESIs and medically attended AEs throughout the study period [Month 0 to Month 18].
Secondary	
To demonstrate the immunological non-inferiority of the MenABCWY vaccine compared to the rMenB+OMV NZ vaccine as measured by the percentages of subjects achieving a 4-fold rise in hSBA titres against *N. meningitidis* serogroup B indicator strains at 1 month after the last MenABCWY vaccination (0,6-months schedule) and 1 month after the rMenB+OMV NZ vaccination (0,2,6-months or 0,6-months or 0,2-months)†	The percentages of subjects with 4-fold rise** in hSBA titres against *N. meningitidis* serogroup B indicator strains at 1 month after the: • last MenABCWY vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • 3-dose vaccination series of rMenB+OMV vaccine(Day 211, Month 7 in MenB_0_2_6 group) or 2-dose vaccination series (Day 211, Month 7 in

Objectives	Endpoints
Criterion: *Non-inferiority will be demonstrated if the LL of the 2-sided 95% CI for the group difference in percentage of subjects achieving a 4-fold rise** in hSBA titres against N. meningitidis serogroup B indicator strains is above -10%.*	MenB_0_6 group) or 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group)† relative to baseline (Day 1, Month 0).
To assess the effectiveness of the rMenB+OMV NZ and MenABCWY vaccines against each of the randomly selected endemic US *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series when compared to 1 month after the MenACWY vaccination.	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group) • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • MenACWY vaccination (Day 31, Month 1 in ACWY group).
To describe the distribution of subjects by percentages of serogroup B invasive disease strains killed using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series of rMenB+OMV NZ and MenABCWY vaccines.	The percentages of serogroup B invasive disease strains killed using enc-hSBA in each subject at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7)
To assess the immune response to the rMenB+OMV NZ (0,2,6-months, 0,6-months and 0,2-months) and MenABCWY (0,6-months) vaccines against *N. meningitidis* serogroup B indicator strains at pre-vaccination (Day 1, Month 0) and at 1 month after the last MenABCWY vaccination and at 1 month after the second and third vaccination of rMenB+OMV NZ.	The immune response to the rMenB+OMV NZ and ABCWY vaccines will be evaluated by measuring bactericidal activity against *N. meningitidis* serogroup B indicator strains as following: *1. The percentages of subjects with hSBA titres ≥ lower limit of quantitation (LLOQ) for each (individual response) and all (composite response) serogroup B indicator strains at baseline (Day 1, Month 0) and at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *2. The percentages of subjects with 4-fold rise** in hSBA titres at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group)

Objectives	Endpoints
	• 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 90, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *relative to baseline (Day 1, Month 0).* *3. hSBA GMTs at baseline (Day 1, Month 0) and at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *4. hSBA GMRs at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *relative to the baseline (Day 1, Month 0).*
To assess the immune response to MenABCWY (0,6-months schedule) and MenACWY (single dose) vaccines against *N. meningitidis* serogroups A, C, W and Y, at pre-vaccination (Day 1, Month 0) and at 1 month after the first and the last MenABCWY vaccination and 1 month after the MenACWY vaccination.	*1. The percentage of subjects with hSBA titres ≥ LLOQ for serogroups A, C, W and Y at baseline (Day 1, Month 0) and:* • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1). *2. The percentage of subjects with 4-fold rise* in hSBA titres at 1 month after the:* • first vaccination (Day 31, Month 1) for the ABCWY group (pooled lots) compared to the MenACWY vaccination in the ACWY group (Day 31, Month 1) *relative to baseline (Day 1, Month 0).* *3. hSBA GMTs against N. meningitidis serogroups A, C, W and Y* at baseline (Day 1, Month 0) and: • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1). *4.hSBA GMRs against N. meningitidis serogroups A, C, W and Y at:* • 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7)

Objectives	Endpoints
	for the ABCWY group (pooled lots) as compared to baseline (Day 1, Month 0), and • 1 month after the single MenACWY vaccination in the ACWY group (Day 31, Month 1) as compared to baseline (Day 1, Month 0). *5.The total IgG as measured by ELISA GMCs against serogroups A, C, W and Y* at baseline (Day 1, Month 0) and*:* • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1).

Abbreviations: ELISA = enzyme-linked immunosorbent assay; Enc-hSBA = endogenous complement human serum bactericidal assay; GMC = geometric mean concentrations; GMT = geometric mean titre; GMR = geometric mean ratio; CI = confidence interval; hSBA = human serum bactericidal assay; LOD: limit of detection; LLOQ = lower limit of quantitation; LL = lower limit; AE = Adverse event; SAE = Serious adverse event; AESI = Adverse event of special interest

N.meningitidis serogroup B indicator strains = M14459, 96217, M13520 and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively.

Refer to Protocol Section 10 for details on evaluation of objectives and sample size justification. Refer to Glossary of terms for definitions of test-based and responder-based effectiveness

^ If the co-primary effectiveness objectives for rMenB+OMV NZ are met, then all objectives for MenABCWY will be evaluated at 95% CI. Refer to Protocol Section 10.1 for details

P† PIf all objectives of rMenB+OMV NZ are met, the comparator will be the 0,2-months schedule. If the 0,2-months objective is not met, and the 0,6-months is met, then the 0,6-months schedule will be the comparator. If the 0,6-months is also not met, then the 0,2,6-months schedule will be the comparator.

*For the Men A, C, W, Y evaluation, the 4-fold rise is defined as:

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

**For the MenB evaluation, the 4-fold rise per each indicator strain is defined as:

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

‡ = post-2nd vaccination for 0,6 and 0,2 schedule and post-3rd vaccination for 0,2,6 schedule.

3. STUDY DESIGN

3.1. Scientific rationale for study design

As the rMenB+OMV NZ licensure in the US was issued through accelerated approval, the FDA has requested to demonstrate the effectiveness of the vaccine against an extended panel of serogroup B meningococcal strains (MenB) as a post-marketing commitment in US adolescents and young adults, thus confirming that the vaccine can protect against diverse meningococcal B strains prevalent in the United States.

The availability of a pentavalent meningococcal vaccine in a single administration would however reduce the number of injections and could increase coverage for meningococcal disease caused by *N. meningitidis* serogroups A, B, C, W, and Y worldwide. GSK's investigational MenABCWY combination vaccine is intended to protect against 5 of the most prevalent serogroups of *Neisseria meningitidis* (A, B, C, W, Y) in humans.

Hence, along with the licensed MenB vaccine (*Bexsero*), this Phase III study will also assess the safety, effectiveness, and immunogenicity of the investigational MenABCWY vaccine.

Rationale for effectiveness assessment

As mentioned above, one of the primary purposes of this study is to evaluate the effectiveness of 2 or 3 doses of rMenB+OMV NZ and of 2 doses of the MenABCWY vaccines in healthy adolescents and young adults by measuring the bactericidal activity against 110 endemic US *N. meningitidis* serogroup B strains using an endogenous complement human Serum Bactericidal Assay (enc-hSBA). Sera from the ACWY group receiving the MenACWY vaccine will also be tested against serogroup B meningococcal strains by enc-hSBA as a control for test-based effectiveness assessment. The overall vaccine effectiveness (VE) against all 110 strains combined will be computed by means of a generalised linear model. For additional details see statistical analysis section of the Clinical Study Protocol (Protocol Section 10).

Rationale for lot-to-lot consistency assessment

MenABCWY is a reconstituted vaccine with the lyophilised 'ACWY component' and liquid rMenB+OMV NZ. The MenB component has the same formulation as the commercial *Bexsero*. To demonstrate that the lots of the investigational MenABCWY vaccine are adequately representative of the formulation intended for marketing, equivalence will be assessed for 3 different lots of the ACWY component of the ABCWY vaccine.

Rationale for non-inferiority assessment of MenABCWY vs MenACWY and rMenB+OMV NZ

The study aims to also demonstrate that the investigational combination MenABCWY vaccine is not inferior to a licensed MenACWY vaccine (*Menveo*) and a licensed MenB vaccine (*Bexsero*) which are part of the current standards of care in the US for prevention of invasive disease caused by *N. meningitidis* serogroups A, C, W, Y and by *N. meningitidis* serogroup B, respectively.

Rationale for blood volume collected:

In order to provide the necessary serum volume for the bactericidal assays (enc-hSBA and/ or hSBA(s)), 25 mL whole blood will be collected at Visit 2, Visit 4 and Visit 6. At pre-vaccination (Visit 1), 20 mL whole blood will be collected to provide the necessary serum volume for the hSBA.

Blood samples are taken from all subjects irrespective of the testing status in order to maintain the study blind. Refer to Protocol Section 8.4.2.1 for further details.

Rationale for the selected vaccination schedules

rMenB+OMV NZ: This study aims at demonstrating the VE of the rMenB+OMV NZ vaccine administered as 2-dose vaccine, either with a shorter interval (0,2-months) or a prolonged interval (0,6-months) between doses. A 3-dose schedule has been also added to better characterise the VE.

Note: The rMenB+OMV NZ in the ACWY group is administered in a 0,1-months schedule. This interval is within the recommendations in the summary of product characteristics of *Bexsero* and helps in maintaining the blind. No objectives are associated with this schedule of rMenB+OMV NZ.

MenABCWY: A number of different vaccine formulations were evaluated in MenABCWY Phase I and II clinical studies. The formulation with the same active ingredient composition as the rMenB+OMV NZ (*Bexsero*) and MenACWY (*Menveo*) vaccines was chosen as the final formulation of the investigational MenABCWY vaccine. Two doses administered 6 months apart (0,6-months) is considered the optimal dosing schedule, based on serogroup B immunogenicity results from MenABCWY Phase II clinical studies.

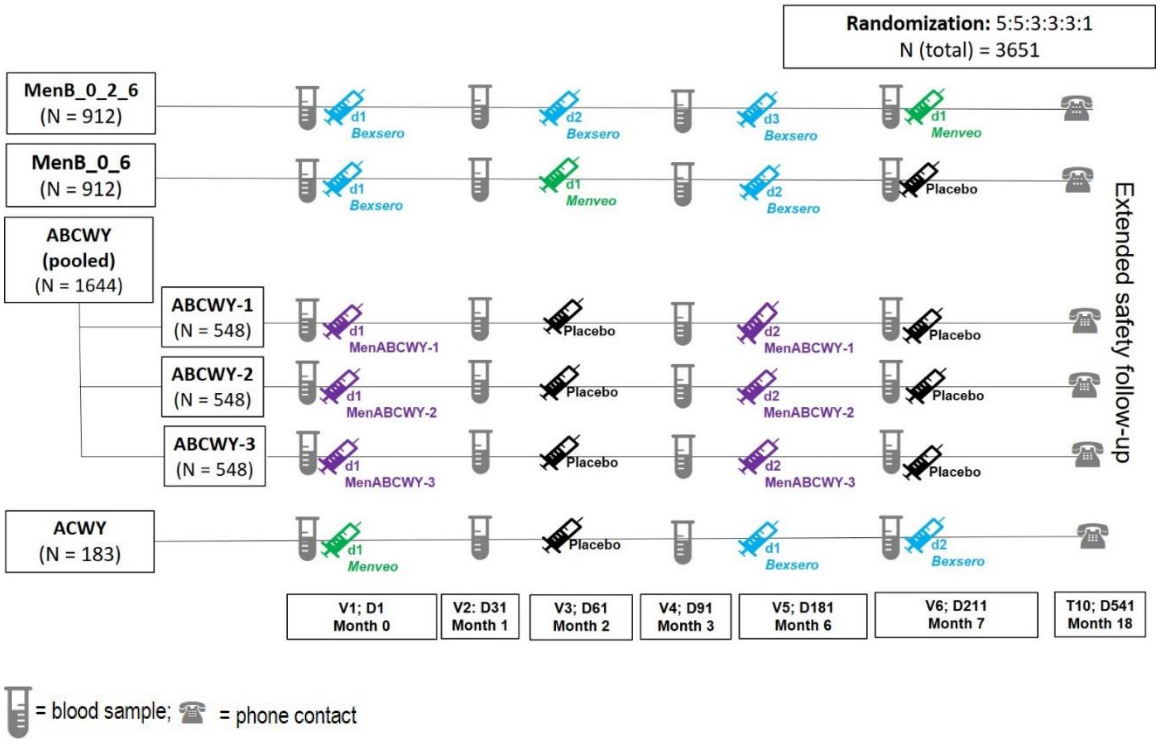
MenACWY: As a comparator for serogroup A, C, W, and Y vaccine effectiveness and immune responses, a single dose of MenACWY vaccine is administered to subjects in the ACWY group. To conform with the standard of care (also in alignment with current ACIP routine immunisation recommendations in US), subjects in the MenB_0_2_6 and MenB_0_6 groups will also receive a dose of MenACWY at Day 211 and Day 61, respectively.

3.1.1. Rationale for the use of placebo

For this study, a placebo (saline solution) will be administered as presented in Figure 1. A placebo is the only available option to minimize possible introduction of reporting bias in collecting information about AEs and to ensure the same number of vaccinations are administered to subjects assigned to either of the six study groups.

3.2. Overall design

Figure 1 Study design overview



N = number of subjects; d = dose; V = visit; D = day; T=Telephone call
Refer to Protocol Table 3 for details on all visits
Note: Home visits may be performed only by sites authorised (as per local regulations and sponsor agreement), with approved site level standard operating procedures (SOP) provided that the compliance with protocol procedures are ensured.

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the schedule of activities (Protocol Section 2), are essential and required for study conduct.

- Type of study: self-contained

- Experimental design: This is a phase III, randomised, controlled, observer-blind, multi-center study to evaluate effectiveness, immunogenicity and safety of rMenB+OMV NZ and MenABCWY vaccines. A total of 3651 healthy adolescents and young adults aged 10-25 years will be enrolled and randomised (5:5:3:3:3:1 ratio) to one of the six parallel study groups:

  – **MenB_0_2_6 group***: subjects will receive 3 doses of rMenB+OMV NZ at Day 1, Day 61 and Day 181 (0, 2 and 0,2,6-months schedule). These subjects will receive 1 dose of the MenACWY vaccine at Day 211**.

  – **MenB_0_6 group**: subjects will receive 2 doses of rMenB+OMV NZ at Day 1 and Day 181 and 1 dose of MenACWY vaccine at Day 61 (rMenB+OMV NZ, 0,6-months schedule). These subjects will receive 1 dose of placebo at Day 211**.

  – **ABCWY-1**: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 1 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211**.

  – **ABCWY-2**: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 2 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211**.

  – **ABCWY-3**: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 3 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211**.

  – **ACWY group**: subjects will receive 1 dose of MenACWY vaccine at Day 1, 1 dose of placebo at Day 61 and 2 doses of rMenB+OMV NZ at Day 181 and Day 211**.

  * MenB_0_2_6 group will also be evaluated for objectives pertaining to 0,2-months vaccination schedule.

  Note 1: A MenB lot will be used for the pre-filled syringe component of the MenABCWY vaccine.

  Note 2: The groups ABCWY-1, ABCWY-2, ABCWY-3 will be pooled into a single group, ABCWY (pooled lots) (except for analysis of lot to lot consistency).

  ** Note 3: In order to let the subjects in MenB_0_2_6 group receive a dose of MenACWY vaccine and for subjects in ACWY group to receive the second dose of rMenB+OMV NZ in line with the vaccine as standard of care (also in line with the Advisory Committee on Immunization Practices (ACIP) recommendations in the US [ACIP, 2011]), the subjects in these groups will receive a vaccination of MenACWY and rMenB+OMV NZ vaccines, respectively, on Day 211 (Visit 6) after completion of the post-vaccination 3 blood sampling. To maintain the blinding of the study, subjects in the rest of the groups (MenB_0_6, ABCWY-1, ABCWY-2 and ABCWY-3) will receive a dose of Placebo. All these vaccines/ product administered at Day 211 are not associated with any study objectives/ endpoints (Safety assessment

conducted after 1 dose of rMenB+OMV NZ in the ACWY group at Day 181 is to maintain the blind of the study).

- Duration of the study: The study duration is approximately 18 months for each subject.
- Primary completion Date (PCD): T10; Day 541.

Refer to Glossary of terms for the definition of PCD.

- End of Study (EoS): the date of release of the last testing results, to be achieved not later than 8 months after Last Subject Last Visit (LSLV) (LSLV = T10; Day 541). If the completion of testing occurs prior the completion of the LSLV the latter date defines the end of study visit.

Refer to Glossary of terms for the definition of EoS.

- Study groups:

Table 2 Study groups and treatment foreseen in the study

Study Groups	Number of subjects	Age (Min-Max)	Treatment name	Vaccine/Product name
MenB_0_2_6	912	10 – 25 y	*Bexsero* (Injection)	rMenB+OMV NZ
			Menveo (Injection)	MenACWY
MenB_0_6	912		*Bexsero* (Injection)	rMenB+OMV NZ
			Menveo (Injection)	MenACWY
			Placebo (Injection)	NaCl
ABCWY-1	548		MenABCWY (with Lot 1 of ACWY) (Injection)	MenABCWY-1
			Placebo (Injection)	NaCl
ABCWY-2	548		MenABCWY (with Lot 2 of ACWY) (Injection)	MenABCWY-2
			Placebo (Injection)	NaCl
ABCWY-3	548		MenABCWY (with Lot 3 of ACWY) (Injection)	MenABCWY-3
			Placebo (Injection)	NaCl
ACWY	183		*Menveo* (Injection)	MenACWY
			Placebo (Injection)	NaCl
			Bexsero (Injection)	rMenB+OMV NZ

Table 3 Overview of study design: Vaccination and Blood Draw Schedule

Visits **Study Day**	**Visit 1** **Day 1**	Visit 2 Day 31	**Visit** 3 **Day 61**	**Visit** 4 **Day 91**	**Visit** 5 **Day 181**	**Visit** 6 **Day 211**
Group **MenB_0_2_6** **N=912**	Pre-vacc Blood sample rMenB+OMV NZ	Post-vacc 1 Blood sample	rMenB+OMV NZ	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample MenACWY
Group **MenB_0_6** **N=912**	Pre-vacc Blood sample rMenB+OMV NZ	Post-vacc 1 Blood sample	MenACWY	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample Placebo
Group **ABCWY-1** **N=548**	Pre-vacc Blood sample MenABCWY-1	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-1	Post-vacc 3 Blood sample Placebo
Group **ABCWY-2** **N=548**	Pre-vacc Blood sample MenABCWY-2	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-2	Post-vacc 3 Blood sample Placebo
Group **ABCWY-3** **N=548**	Pre-vacc Blood sample MenABCWY-3	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-3	Post-vacc 3 Blood sample Placebo
Group **ACWY** **N=150**	Pre-vacc Blood sample MenACWY	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample rMenB+OMV NZ

N = number of subjects; Pre-vacc = pre-vaccination; Post-vacc = post-vaccination

- Treatment allocation: At Day 1, prior to the study vaccination, subjects will be randomised to 1 of the 6 study groups according to a 5:5:3:3:3:1 ratio.
- Blinding: Observer-blind. Kindly refer to Protocol Section 7.3 for details on blinding and unblinding procedures.
- Sampling schedule:
  - A total of 4 blood samples* will be collected from each subject at Day 1 (pre-vaccination blood sample; approximately 20 mL), at Day 31 (post-vaccination 1 blood sample; approximately 25 mL), at Day 91 (post-vaccination 2 blood sample; approximately 25 mL) and at Day 211 (post-vaccination-3 blood sample; approximately 25 mL).
  - Urine sampling: Urine samples for pregnancy testing will be collected from female subjects of child-bearing potential at Visit 1 (Day 1), Visit 3 (Day 61), Visit 5 (Day 181) and Visit 6 (Day 211) prior to the vaccination.

  * Insufficient blood volume may lead to test cancellation and jeopardise the statistical power. Hence, every effort must be done to collect blood volume as per protocol requirements.
- Data collection: standardised Electronic Case Report Form (eCRF). Solicited symptoms will be collected using a subject Diary (electronic Diary [eDiary]).
- Safety monitoring: Regular safety follow-up will be done through telephone calls (T). There will also be an extended safety follow-up (ESFU) phone call 12 months post-vaccination 3 (Day 181; Visit 5). This ESFU phone call will also mark the study conclusion. Refer to Protocol Table 3 and Protocol Section 8.5.3 for details on the safety follow-up.

3.3. Number of subjects

A total of 3651 subjects will be randomised in a ratio of 5:5:3:3:3:1; 912 each in MenB_0_2_6 and MenB_0_6 groups, 548 in each ABCWY groups and 183 in ACWY group. Assuming a 25% drop out rate, this should provide approximately 684 evaluable subjects in each of the MenB groups, 411 evaluable subjects in each of the ABCWY groups and 137 evaluable subjects in the ACWY group.

Refer to Protocol Section 10.1 for a detailed description of the criteria used in the determination of sample size.

Withdrawals will not be replaced.

3.4. Subject and study completion

A subject is considered to have completed the study, if the subject is available for the concluding contact (T10; Day 541) as described in the protocol.

Global completion of the study is required in order to provide enough subjects as defined in Protocol Section 10.1 Sample Size Determination.

4. ANALYSIS SETS

4.1. Definition

For purposes of analysis, the following analysis sets are defined:

4.1.1. Enrolled Set

Subject/ Subject for whom parent(s)/LAR's agreed to participate in a clinical study after completion of the informed consent process, who meet screening/eligibility criteria and randomized and/or received study intervention or undergone an invasive procedure.

4.1.2. Exposed Set

All subjects who received at least 1 dose of the study treatment. The allocation in a group is done in function of all administered treatments.

4.1.3. Full Analysis Set

All subjects who received at least 1 dose of the study treatment and have post-vaccination effectiveness or immunogenicity data.

4.1.4. Per Protocol Set

All subjects in the Full Analysis Set minus subjects with protocol deviations that lead to exclusion from the Per Protocol Set.

4.1.5. Solicited Safety Set

All subjects who received at least 1 dose of the study treatment (Exposed Set) who have solicited safety data beyond 30 minutes post vaccination.

4.1.6. Unsolicited Safety Set

All subjects who received at least 1 dose of the study treatment (Exposed Set) that report unsolicited AEs/report not having unsolicited AEs.

4.1.7. Overall Safety Set

All subjects that belong to the Unsolicited safety or/and to the Solicited safety set.

4.2. Criteria for eliminating data from Analysis Sets

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

4.2.1. Elimination from Exposed Set (ES)

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

4.2.2. Elimination from Per protocol Set (PPS)

4.2.2.1. Excluded subjects

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

Table 4 Elimination code and condition to exclude a subject from the PPS analysis

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
800	Fraudulent data	All	All
900	Invalid informed consent	All	All
1030	Study vaccine not administered at all	All	All
1050	Randomization failure	Visit 1, 3, 5	All
1060	Randomization code was broken	All	All
1070.1	Subjects got vaccinated with the correct vaccine but containing a lower volume	Visit 1, 3, 5	All
1070.2	Vaccination not according to protocol	Visit 1, 3, 5	All
1080	Vaccine temperature deviation	Visit 1, 3, 5	All
1090	Expired vaccine administered	Visit 1, 3, 5	All
1500.1	Other deviation from study procedures not able to classified under any other categories	All	All
1500.2	Any other GCP non-compliance not able to classified under any other categories	All	All
2010	Protocol violation (inclusion/exclusion criteria)	All	All
2040	Administration of any medication forbidden by the protocol	Visit 1, 3, 5	All
2050	Not withdrawn after developing withdrawal criteria other than prohibited concomitant vaccination/medication (medical condition forbidden)	All	All
2060	Concomitant infection related to the vaccine which may influence immune response (only meningococcal infection)	All	All
2080	Subjects did not comply with vaccination schedule	Visit 3, 5	All

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
2090	Subjects did not comply with blood sample schedule	Visit 2, 4, 6	All
2100	Serological results not available post-vaccination for all tests	Visit 2, 4, 6	All
2120	Obvious incoherence or abnormality or error in data related to testing	Visit 2, 4, 6	All
2130	Biological sample specimen procedures not compliant with protocol	Visit 2, 4, 6	All

4.2.3. Elimination from unsolicited and solicited safety set

4.2.3.1. Excluded subjects

4.2.3.1.1. Unsolicited safety set

Code 1030 (Study vaccine not administered at all), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1150 (no post-vaccination safety data) will be used for identifying subjects eliminated from the unsolicited safety set.

4.2.3.1.2. Solicited safety set

Code 1030 (Study vaccine not administered at all), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1160 (no post-vaccination solicited safety data) will be used for identifying subjects eliminated from the solicited safety set.

5. STATISTICAL ANALYSES

Standard data derivation rules and statistical methods are described in section 10.1 while the study specific data derivation rules and stat methods are described in section 9.

5.1. Disposition of subjects

5.1.1. Analysis of disposition of subjects planned in the protocol

Number of subjects enrolled, vaccinated subjects (at least 1 vaccination, full vaccination course), reason for early withdrawal, FAS, and PPS will be described by vaccine group.

5.1.2. Additional considerations

Not applicable

5.2. Demography and baseline characteristics analyses

5.2.1. Analysis of demography and baseline characteristics planned in the protocol

Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age, height, weight, and body mass index (BMI) at enrolment will be calculated overall and by vaccine group.

Distributions of subjects by sex, race, ethnic origin will be summarised overall and by vaccine group.

5.2.2. Additional considerations

A summary table of important protocol deviations related to COVID-19 will be provided. Also, a listing will be produced.

5.3. Primary effectiveness and immunogenicity

5.3.1. Analysis of primary effectiveness and immunogenicity planned in the protocol

Refer to Glossary of terms for definitions of test-based and responder-based vaccine effectiveness. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then all objectives for MenABCWY will be evaluated at 95% CI (Sections 5.3.1.7 through 5.3.1.11, ref Protocol Section 10.1).

5.3.1.1. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Analysis set: Per-protocol set (PPS) will be the primary analysis population

Statistical method: The VE is defined as 1- RR= (1- percentage of samples without bactericidal serum activity at 1:4 dilution in MenB group / percentage of samples without bactericidal serum activity at 1:4 dilution in the ACWY group) x100% and it will be analyzed using a generalised linear model with vaccine group, strain, and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) as independent variables. Furthermore, a repeated statement will be used to estimate the variance of the RR including correlation within subject's responses to different strains. If the statistical model does not converge due to (one of) the factor(s), a model without this/these factor(s) will be fitted instead. The response variable of the model will be the Bernoulli distributed outcome without bactericidal activity at a 1:4 dilution (i.e. response is 1 if titre < 4, and 0 if titre ≥ 4), at 1 month after the last vaccination (Month 7) in the MenB group and at Month 1 for the ACWY group. Each subject will contribute with approximately 35 measures to this analysis, each of the measures corresponding to the response variable to one of the 35 strains randomly assigned to be tested with the samples available for that specific subject.

In order to obtain the VE measure which is a measure based on the relative risk (RR), a generalised linear model will be used with the Binary distribution and link function log in order to compute the log RR and the corresponding 97.5% CI. The obtained values will be exponentiated to obtain the RR and the corresponding 97.5% CI. The VE will be computed as 100% x (1 – RR). Effectiveness of rMenB+OMV NZ (0,2,6-months schedule) will be demonstrated if the lower limit of the two-sided 97.5% CI for VE between MenB and the ACWY group is above 65%.

5.3.1.2. Effectiveness (Responder-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Analysis set: FAS will be the primary analysis population.

Statistical method: The percentage of responders (see definition in Glossary of terms) and the corresponding exact two-sided 97.5% CI based on Clopper-Pearson method will be calculated [Clopper, 1934].

The objective is to demonstrate that the lower limit of the 97.5% CI for the percentage of responders is higher than 65%.

5.3.1.3. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 5.3.1.1

5.3.1.4. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 5.3.1.2

5.3.1.5. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 5.3.1.1

5.3.1.6. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 5.3.1.2

5.3.1.7. Lot-to-lot consistency: MenABCWY - ACWY component

Analysis set: The analysis of lot-to-lot consistency will be based on the PPS.

Statistical method: For each of the three ABCWY lots (Lots 1, 2 and 3 of the MenACWY component of the ABCWY vaccine), GMTs and 97.5% CIs will be calculated by exponentiating (base 10) the least squares means and the lower and upper limits of the 97.5% CIs of the log transformed titres (base10) obtained from an Analysis of Variance

(ANOVA) with factors for vaccine lot and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)). Additionally, lot-to-lot GMT ratios will be computed for each pair of ABCWY lots. Ninety-seven point five percent (97.5%) CIs for the ratios of GMTs will be constructed by exponentiating the difference of the least square means of the log transformed titres and the lower and upper limits of the 97.5% CIs on the difference obtained from the ANOVA model above.

Lot-to-lot consistency criterion: The three ABCWY lots will be considered equivalent if for each of the 4 serogroups A, C, W and Y and each pair of vaccine lots, the two-sided 97.5% CI on the ratio of GMTs at 1 month after the last vaccination will be contained within the interval [0.5, 2.0].

If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.1.8. Immunological non-inferiority: MenABCWY vs. MenACWY

Analysis set: PPS restricted to subjects without previous ACWY vaccination will be the primary analysis population.

Statistical method: The percentage of subjects with 4-fold riseP*P in hSBA titres against MenACWY indicator strains A, C, W and Y and the corresponding exact two-sided 97.5% CIs based on Clopper-Pearson method will be calculated for the ABCWY (pooled lots) group and the ACWY group [Clopper, 1934]. The 97.5% CIs for the difference in percentages between ABCWY (pooled lots) and ACWY group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-Inferiority criterion: Non-inferiority of MenABCWY vaccine for the proportion of subjects with 4-fold rise will be demonstrated if the lower limit of the two-sided 97.5% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY (pooled) lots –ACWY) is above -10%.

* For the Men A, C, W, Y evaluation, the 4-fold rise is defined as:

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

Table 5 reads the LOD and LLOQ of MenACWY indicator strains used in the definition of 4-fold rise provided by the laboratory.

Table 5 LOD, LLOQ, and ULOQ of MenACWY indicator strains

Strain	LOD	LLOQ	ULOQ
Men A (3125)	CCI [redacted]		
Men C (C11)			
Men W (240070)			
Men Y (860800)			

If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.1.9. Vaccine effectiveness (Test-based): MenABCWY

See Section 5.3.1.1. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the VE for MenABCWY will be evaluated at 95% CI.

5.3.1.10. Effectiveness non-inferiority: MenABCWY vs. rMenB+OMV NZ

Analysis set: PPS will be the primary analysis population.

Statistical method: The percentage of samples with bactericidal activity measured by enc-hSBA at 1:4 dilution and the corresponding exact two-sided 97.5% CIs based on Clopper-Pearson method will be calculated for the ABCWY (pooled lots) group and the MenB group comparator that will be selected (ref: the footnote of Figure 2). The 97.5% CIs for the difference in percentages between ABCWY (pooled lots) and selected MenB group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-Inferiority criterion: Non-inferiority of MenABCWY vaccine for the percentage of samples with bactericidal activity measured by enc-hSBA at 1:4 dilution will be demonstrated if the lower limit of the two-sided 97.5% CI for the difference between the 2 groups (ABCWY (pooled) lots – MenB) is above -5%.

If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.1.11. Effectiveness (Responder-based): MenABCWY

See Section 5.3.1.2. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the effectiveness (responder-based) for MenABCWY will be evaluated at 95% CI.

5.3.2. Additional considerations

Analyses of the primary effectiveness and immunogenicity objectives will be repeated by age group (10-17 years of age and 18-25 years of age), race, sex, region (US/ ex-US), and subjects with and without a previous MenACWY vaccination (primed and unprimed).

5.3.2.1. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

The SAS code to analyse the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) objective is specified below. Treatment, region, age category, previous ACWY vaccination, and strains will be modelled as fixed effect. To account for a possible over-dispersion, the DSCALE option in the model statement will be evaluated first. The DSCALE will be kept in the model only if the F-statistics for the DSCALE parameter is significant ($p<0.05$). The following SAS code will be used for the VE calculation:

```
ods trace on;
ods output GEEEmpPEst = genmod_stats
CONVERGENCESTATUS = converge ;

PROC GENMOD data=dataset descending;
class trtgrp strain region agecat previousACWY subject_id ;
model outcome = trtgrp strain region agecat previousACWY / dist= bin
link= log DSCALE;
repeated subject = subject_id / type= CS withinsubject= strain;
estimate 'MenB026-ACWY' trtgrp 1 0 0 0 0 -1/ alpha=0.025 exp;

/*trtgrp R is MenB0,2,6 and trtgrp W is ACWY*/

run;

ods output close;

data genmod_stats;
set genmod_stats;
where parm = 'trtgrp' and level1 = '1';
rr = exp(estimate);
ub = exp(uppercl);
ve = (1 - rr)*100 ;
ve_ll = (1 - ub) * 100 ;
if ve_ll > 65 then success = 1 ;
else success = 0 ;
run;
```

where outcome represents the Bernoulli distributed outcome without bactericidal activity at a 1:4 dilution (i.e. response is 1 if titre < 4, and 0 if titre ≥ 4), one month after the 3rd vaccination in MenB 0,2,6 and one month after the MenACWY vaccination for the ACWY arm, trtgrp indicates the vaccine groups, strain is the serogroup B strain variable, region is either US or ex-US, agecat is the age at enrolment (10-17 YoA or 18-25 YoA), and previousACWY is previous ACWY vaccination (y/n) at enrolment.

rr is the relative risk (RR), which is obtained from the estimated parameters from PROC GENMOD. Vaccine effectiveness (VE) is then derived as (1-rr)x100%.

ub represents the upper bound of the 97.5% CI of the relative risk. ve_ll is the lower bound of the 97.5% CI for VE, if the value is greater than 65%, then the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) objective is successful.

5.3.2.2. Effectiveness (Responder-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Not applicable

5.3.2.3. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 5.3.2.1, with the difference in the treatment arm:

```
PROC GENMOD data=dataset descending;
class trtgrp strain region agecat previousACWY subject_id ;
model outcome = trtgrp strain region agecat previousACWY / dist= bin
link= log DSCALE ;
repeated subject = subject_id / type= CS withinsubject= strain ;
estimate 'MenB06-ACWY' trtgrp 0 1 0 0 0 -1/ alpha=0.025 exp;

/*trtgrp S is MenB0,6 and trtgrp W is ACWY*/

run;
```

5.3.2.4. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

Not applicable

5.3.2.5. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 5.3.2.1, with the difference the outcome data for group R is from one month after the 2nd vaccination instead of one month after the 3rd vaccination.

5.3.2.6. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

Not applicable

5.3.2.7. Lot-to-lot consistency: MenABCWY - ACWY component

Not applicable

5.3.2.8. Immunological non-inferiority: MenABCWY vs. MenACWY

As a sensitivity analysis, a parametric model will be run. A generalized linear model with factors for vaccine group and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA)) will be ran, with the Binary distribution and link function is identity, and outcome is 4-fold rise. If the lower limit of the two-sided 97.5% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY (pooled) lots –ACWY) coming from the model is above -10%, also the sensitivity analysis has demonstrated non-inferiority. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.2.9. Vaccine effectiveness (Test-based): MenABCWY

See Section 5.3.2.1, with the difference in the estimate statement:

```
PROC GENMOD data=dataset descending;
class trtgrp strain region agecat previousACWY subject_id ;
model outcome = trtgrp strain region agecat previousACWY / dist= bin
link= log DSCALE ;
repeated subject = subject_id / type= CS withinsubject= strain ;
estimate 'MenABCWY-ACWY' trtgrp 0 0 1 1 1 -3/ alpha=0.025 exp
divisor=3;

/*trtgrp T, U, and V are the ABCWY-1, ABCWY-2, and ABCWY-3 lots and
trtgrp W is ACWY*/
run;
```

5.3.2.10. Effectiveness non-inferiority: MenABCWY vs. rMenB+OMV NZ

As a sensitivity analysis, a parametric model will be run. A generalized linear model with factors for vaccine group and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) will be ran, with the Binary distribution and link function is identity, and outcome is bactericidal activity measured by enc-hSBA at 1:4 dilution. If the lower limit of the two-sided 97.5% CI for the difference in percentage of samples with bactericidal activity measured by enc-hSBA at 1:4 dilution between the 2 groups (ABCWY (pooled) lots –MenB) coming from the model is above -5%, also the sensitivity analysis has demonstrated non-inferiority. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

In addition to the comparison of MenABCWY vs the selected MenB schedule per Section 5.3.1.10, MenABCWY will be compared to the other MenB schedule/schedules, whichever is applicable in the same way as described in Section 5.3.1.10. If MenB 0,2 schedule is selected as comparator, in addition MenABCWY will be compared to Menb 0,6 and MenB 0,2,6 schedule. If MenB 0,6 schedule is selected as comparator, in addition MenABCWY will be compared to MenB 0,2,6 schedule. No success criterion is defined for these group comparisons.

5.3.2.11. Effectiveness (Responder-based): MenABCWY

Not applicable

5.4. Secondary effectiveness and immunogenicity

5.4.1. Analysis of secondary effectiveness and immunogenicity planned in the protocol

5.4.1.1. Immunological non-inferiority: MenABCWY vs. rMenB+OMV NZ

Analysis set: PPS will be the primary analysis population.

Statistical method: The percentages of subjects with 4-fold rise* in hSBA titres against N. meningitidis serogroup B indicator strains (M14459, 96217, M13520 and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively) at 1 month after the last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) and 1 month after the 3-dose vaccination series (Day 211, Month 7) in MenB_0_2_6 group or 2-dose vaccination series (Day 211, Month 7) in MenB_0_6 group or 2-dose vaccination series (Day 91, Month 3) in MenB_0_2_6 group and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated [Clopper, 1934]. The 95% CIs for the difference in percentages between ABCWY group (pooled lots) and MenB_0_2_6 group and MenB_0_6 group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-inferiority criterion: Non-inferiority of MenABCWY vaccine for the proportion of subjects with 4-fold rise will be demonstrated if the lower limit of the 2-sided 95% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY group (pooled lots) –selected MenB group) is above -10%.

* For the MenB evaluation, the 4-fold rise per each indicator strain is defined as:

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

‡ = post-2nd vaccination for 0,6 and 0,2 schedule and post-3rd vaccination for 0,2,6 schedule).

Table 6 reads the LOD and LLOQ of hSBA titres against N. meningitidis serogroup B indicator strains used in the definition of 4-fold rise provided by the laboratory.

Table 6 LOD and LLOQ of hSBA titres against N. meningitidis serogroup B indicator strains

Strain	LOD	LLOQ
NZ98-254	CCI [redacted]	
96217		
M14459		
M13520		

5.4.1.2. Effectiveness by each of the endemic US N. meningitidis serogroup B strains

Analysis set: FAS will be the primary analysis population. The ABCWY (pooled lots) group and the MenB group comparator that will be selected (ref: the footnote of Figure 2) will be used for the purpose of this analysis.

Statistical method: The VE per strain will be calculated as described in Section 5.3.1.1, using a generalised linear model with vaccine group, and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) as independent variables, and alpha=0.05 leading to 95% CI. In case for a strain 100% response will be observed in both vaccine groups, VE against these strain will be assessed by calculating 95% CI for relative risk from raw proportions, and VE=1-RR.

5.4.1.3. Distribution of percentages of serogroup B invasive disease strains killed

Analysis set: FAS will be the primary analysis population. The ABCWY (pooled lots) group and the MenB group comparator that will be selected (ref: the footnote of Figure 2) will be used for the purpose of this analysis.

Statistical method: Summary statistics of the percentage of serogroup B invasive disease strains killed within a subject using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series of rMenB+OMV NZ and MenABCWY vaccines.

Summary statistics and 95% CI for the mean percentage will be presented, as well as a Figure of the cumulative distribution function.

5.4.1.4. Immune response of MenABCWY, rMenB+OMV NZ and MenACWY

Analysis set: The analysis will be based on the FAS.

Statistical method: The hSBA titres at each time point for all groups (ABCWY group (pooled lots), MenB_0_2_6 and MenB_0_6 groups) will be logarithmically transformed (base10) to fulfil the normal distribution assumption. For each N. meningitidis serogroup A, C, W and Y and each B indicator strain (M14459, 96217, M13520 and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively), the GMTs and GMRs (post-vaccination/baseline) will be obtained from an Analysis of Variance (ANOVA) with factors for vaccine group, region (US/ex-US), age category (10-17 YoA/18-25 YoA), and previous MenACWY vaccination (y/n), and then exponentiating the log-transformed means and their 95% CIs. The ratio of GMTs and GMRs between two groups and the corresponding CI will be estimated additionally.

The total IgG (as measured by ECL) against serogroups A, C, W and Y at baseline (Day 1, Month 0) and

- at 1 month after the first (Day 31, Month 1) and the last vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and
- at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1),

will be analyzed in a comparable way as described above for hSBA titres. Since total IgG is measured as concentration instead of titer, the resulting geometric mean of the concentrations is abbreviated as GMC.

Table 7 LLOQ and ULOQ of total IgG (as measured by ECL) MenACWY indicator strains

Strain	LLOQ	ULOQ
Men A	CCI	
Men C		
Men W		
Men Y		

For each N. meningitidis A, C, W and Y and for each (individual response) and all (composite response) serogroup B indicator strain (M14459, M13520, 96217 and NZ98/254) the percentages of subjects with hSBA titres ≥LLOQ and of subjects with 4-fold rise and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated for each study group at each timepoint not previously analyzed. Ninety-five percent (95%) CIs for the difference in percentages between ABCWY (pooled lots) on the one hand and MenB_0_2_6, MenB_0_6, and ACWY groups, respectively, on the other hand, will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

For each N. meningitidis serogroup A, C, W and Y, analyses of hSBA GMTs, percentages of subjects with hSBA titres ≥LLOQ and of subjects with 4-fold rise, will be repeated by subjects with and without a previous MenACWY vaccination (primed and unprimed). Similarly, analyses of GMCs of the total IgG (as measured by ECL) against serogroups A, C, W and Y will be repeated by subjects with and without a previous MenACWY vaccination (primed and unprimed).

5.4.1.5. Cohen kappa level of agreement

The human serum bactericidal assay (hSBA) and the endogenous complement human serum bactericidal assay (enc-hSBA) provide two different types of results for B strains; the hSBA gives a quantitative, continuous result (hSBA titer) while the enc-hSBA gives a qualitative, categorical result (with/without bactericidal activity).

To assess the agreement between hSBA and enc-hSBA, the Kappa statistics [Cohen, 1960] will be used and the hSBA results will be categorized as follows:

- The hSBA will be categorized as <LLOQ and ≥LLOQ (Ref. Table 6). Agreement will be assessed versus the positive and negative categories of the enc-hSBA at 1:4 dilution.

To evaluate the strength of the agreement, the following scale [Landis, 1977] will be used:

Table 8 Strength of agreement scale

Kappa	Strength of Agreement
< 0.00	Poor
0.00-0.20	Slight
0.21-0.40	Fair
0.41-0.60	Moderate
0.61-0.80	Substantial
0.81-1.00	Almost Perfect

A 95% Confidence Interval (CI) will be provided together with the point estimate of the Kappa for each of the above situations. The McNemar test will be also performed using the same categorizations of the hSBA results as described above. The aforementioned comparisons/tests will be all performed overall across vaccine groups, separately for each serogroup B test strain. The following SAS code will be used for the Kappa calculation and the McNemar test:

```
PROC FREQ data=dataset;
table assay1_res*assay2_res / agree;
run;
```

where assay1_res represents the enc-hSBA result, assay2_res represents the precategorized hSBA result.

5.4.2. Additional considerations

5.4.2.1. Immunological non-inferiority: MenABCWY vs. rMenB+OMV NZ

As a sensitivity analysis, a parametric model will be run. A generalized linear model with factors for vaccine group and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) will be ran, with the Binary distribution and link function is identity, and outcome is 4-fold rise. If the lower limit of the two-sided 95% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY (pooled) lots –MenB) coming from the model is above -10%, also the sensitivity analysis has demonstrated non-inferiority.

5.4.2.2. Effectiveness by each of the endemic US N. meningitidis serogroup B strains

The SAS code to analyse the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) by strain is specified below. Treatment, and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) will be modelled as fixed effect. To account for a possible over-dispersion, the DSCALE option in the model statement will be evaluated first. The DSCALE will be kept in the model only if the F-statistics for the DSCALE parameter is significant ($p<0.05$). The following SAS code will be used for the VE calculation:

```
ods trace on;
ods output  GEEEmpPEst = genmod_stats
CONVERGENCESTATUS = converge ;

PROC GENMOD data=dataset descending;
class trtgrp region agecat previousACWY;
by strain ;
model outcome = trtgrp region agecat previousACWY / dist= bin link= log
DSCALE alpha=0.05;
estimate 'MenB026-ACWY' trtgrp 1 0 0 0 0 -1/ alpha= 0.05 exp;

/*trtgrp R is MenB0,2,6 and trtgrp W is ACWY*/

run;

ods output close;

data genmod_stats;
set genmod_stats;
by strain ;
where parm = 'trtgrp' and level1 = '1';
rr = exp(estimate);
ub = exp(uppercl);
ve = (1 - rr)*100 ;
ve_ll = (1 - ub) * 100 ;
if ve_ll > 65 then success = 1 ;
else success = 0 ;
run;
```

where outcome represents the Bernoulli distributed outcome without bactericidal activity at a 1:4 dilution (i.e. response is 1 if titre < 4, and 0 if titre ≥ 4), one month after the 3rd vaccination in MenB0,2,6 and one month after the MenACWY vaccination for the ACWY arm, trtgrp indicates the vaccine groups, strain is the serogroup B strain variable, region is either US or ex-US, agecat is the age at enrolment (10-17 YoA or 18-25 YoA), and previousACWY is previous ACWY vaccination (y/n) at enrolment.

rr is the relative risk (RR), which is obtained from the estimated parameters from PROC GENMOD. Vaccine effectiveness (VE) is then derived as (1-rr)x100%.

ub represents the upper bound of the 95% CI of the relative risk. ve_ll is the lower bound of the 95% CI for VE, if the value is greater than 65%, then the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) objective is successful.

In summary in case of convergence issue the following hierarchical decision tree will be applied

- Binary model including region, agecat, and previousACWY
- Binary model, excluding region, agecat, and previousACWY
- Cochran-Mantel-Haenszel (CMH) method (if strain has 100% killed or 0% killed for ANY treatment)
- VE set to 0% (if strain has 100% killed for both treatment)

5.4.2.3. Distribution of percentages of serogroup B invasive disease strains killed

Not applicable

5.4.2.4. Immune response of MenABCWY, rMenB+OMV NZ and MenACWY

Not applicable

5.5. Safety and reactogenicity

5.5.1. Analysis of safety and reactogenicity planned in the protocol

Distribution of subjects by vaccinations will be summarised by vaccine group for the Enrolled Set. In case of vaccination error, subjects will be analyzed “as treated” (according to the vaccine the subject received).

Analysis sets: Solicited Safety Set (solicited local and systemic adverse events and other solicited adverse events), Unsolicited Safety Set (unsolicited adverse events), and Overall Safety Set.

Endpoint	Statistical Analysis Methods
Primary	**Endpoints description**: The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) adverse events during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. All solicited adverse events will be summarised according to defined severity grading scales, see protocol section 12.5.9.3. Frequencies and percentages of subjects experiencing each adverse event will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic adverse event overall and at each time point will also be presented. Post-vaccination solicited adverse events reported from Day 1 to Day 7 will be summarised for the intervals Day 1-3, Day 4-7, and Day 1-7 by maximal severity and by vaccine group, excluding the 30-minute measurement, which will be summarised separately. The severity of solicited local adverse events, including redness (erythema) at injection site, swelling of skin at injection site, and hardness of skin at injection site will be summarised according to categories based on linear measurement: None (1 to 24mm); Mild (25 to 50mm); Moderate (51 to 100mm); Severe (>100mm). Injection site tenderness and systemic reactions (except fever) occurring up to 7 days after each vaccination at Day 1, Day 61 and Day 181 will be summarised according to "mild", "moderate" or "severe". Each solicited local and systemic adverse event will also be further summarised as "none" versus "any" (for fever the latter will be ≥38.0 °C). Use of antipyretics and analgesics will be summarised by frequency by type of use (prophylactic versus treatment) and percentage of subjects reporting use. Body temperature will be summarised 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 temperatures ≥ 38.0 °C and temperatures ≥ 40.0 °C will also be presented.
	Endpoints description: The frequencies and percentages of subjects with any unsolicited ***AEs*** (including all SAEs), ***AEs*** leading to withdrawal and medically attended ***AEs*** during the 7 and the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. The frequencies and percentages of subjects with SAEs, ***AEs*** leading to withdrawal***, AESIs*** and medically attended ***AEs*** throughout the study period. This analysis applies to all adverse events occurring during the study, judged either as possibly related, or not related to vaccination by the investigator, recorded in AE CRF, with a start date on or after the date of first vaccination. AE starting prior to the first vaccination will only be listed. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class. All reported adverse events, as well as adverse events judged by the investigator as possibly related to study vaccine, will be summarised 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 adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted. Separate summaries will be produced for the following categories: • Serious adverse events. • Adverse events that are possibly related to vaccine. • Adverse events of special interest. • Adverse event leading to withdrawal. • Adverse events leading to a medically attended visit. Data listings of all adverse events will be provided by subject. In addition, adverse events in the categories above will be provided as listed data. Local and systemic AEs will be analyzed by point estimates with associated 95% CIs [Clopper, 1934].

5.5.2. Additional considerations

For analyses of the safety and reactogenicity endpoints, subjects will be analyzed "as treated" according to the actual vaccination a subject received.

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

Analyses of safety objectives will be repeated by age group (10-17 years of age and 18-25 years of age), race, sex, region (US/ ex-US), and with and without a previous MenACWY vaccination (primed and unprimed).

A Table and Listing of COVID-19 AE cases will be provided.

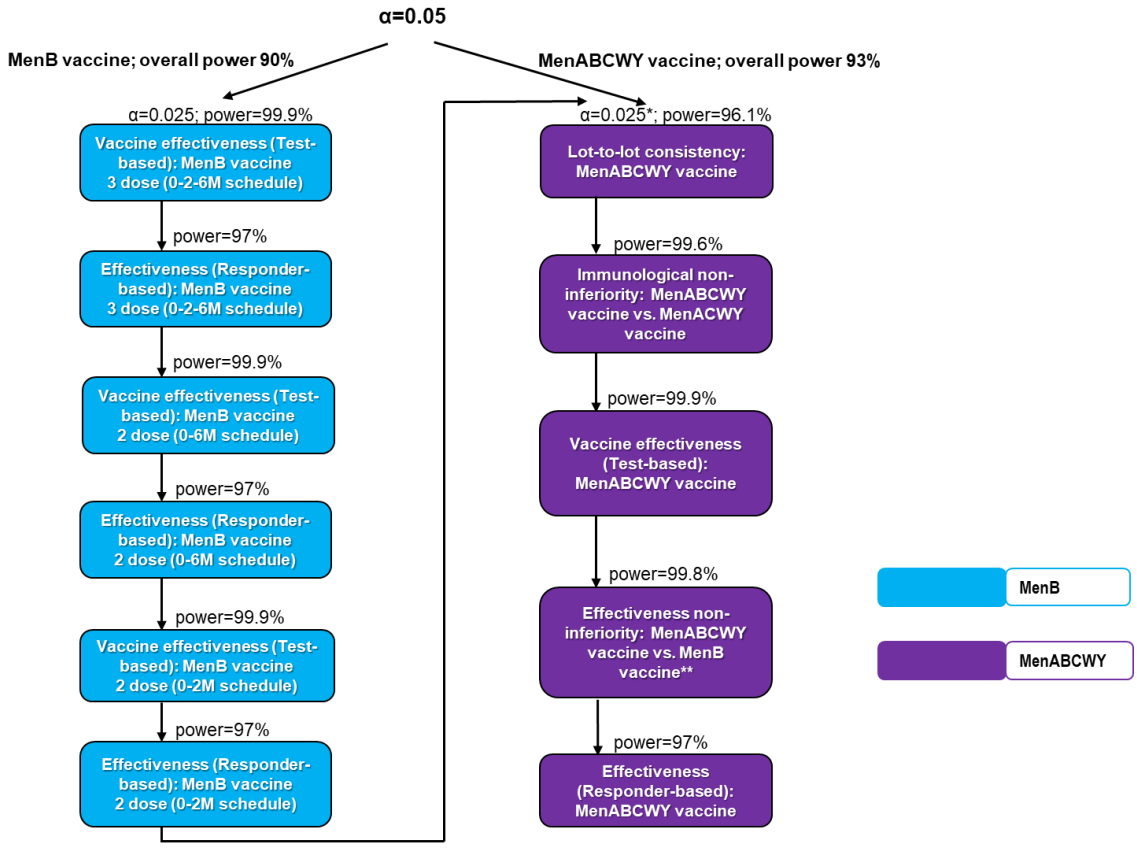
In case for a subject besides ediary data, also solicited reactions were recorded in the CRF, the CRF data will be mapped into the SDTM data with the ediary data (FA domain). For the analysis, the CRF data will be used in case of duplicate data.

6. ANALYSIS INTERPRETATION

Multiple objectives and endpoints require type I error control. Full alpha (0.05) is split equally (alpha=0.025) between rMenB+OMV NZ objectives and MenABCWY objectives. Furthermore, within rMenB+OMV NZ, as well as within MenABCWY, objectives are tested hierarchically. If the first null hypothesis is rejected, then the testing will continue with the second hypothesis at same alpha. Same for 3rd, 4th, and so forth. Whenever a null hypothesis is not rejected, then the testing will stop.

As the comparator for MenABCWY non inferiority objective for the B component will be the selected schedule of rMenB+OMV NZ as determined in this study, the objectives of rMenB+OMV NZ will be analysed first. Additionally, if all null hypotheses related to rMenB+OMV NZ objectives will be rejected, the alpha (alpha=0.025) will be propagated to the MenABCWY part, and hypotheses related to MenABCWY objectives will be tested at full alpha (alpha=0.05). See Figure 2 for an explanation of the hierarchical testing (top to bottom, the order indicated by the arrows).

Figure 2 Hierarchical testing of hypothesis



* Alpha split equally between rMenB+OMV NZ and MenABCWY vaccine objectives.
If all rMenB+OMV NZ objectives achieved, MenABCWY vaccine objectives will be tested at full alpha.
** If all objectives of rMenB+OMV NZ are met, the comparator will be the 0,2-months schedule. If the 0,2-months objective is not met, and the 0,6-months is met, then the 0,6-months schedule will be the comparator. If the 0,6-months is also not met, then the 0,2,6-months schedule will be the comparator.

Refer to Glossary of terms for definitions of test-based and responder-based vaccine effectiveness.

7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

The final study report will contain at least the final analyses of all primary and secondary endpoints.

7.2. Statistical considerations for interim analyses

No interim analysis is planned for this study

8. CHANGES FROM PLANNED ANALYSES

Not applicable

9. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

The following sections describe additional derivation rules and statistical methods which are not presented in section 10.1.

9.1. Data derivation

Not applicable

9.2. Statistical Method

Not applicable

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

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

10.1.1. Attributing events to vaccine doses

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

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

10.1.2. Handling of missing data

10.1.2.1. Dates

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

- A missing day will be replaced by 15

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

The following exceptions apply:

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

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

10.1.2.2. Laboratory data

Missing laboratory results (including immunological data) will not be replaced.

10.1.2.3. Daily recording of solicited adverse events

10.1.2.3.1. Studies with electronic diaries

For studies using electronic diaries for the collection of solicited adverse events, a solicited adverse events will be considered present only when a daily recording of grade 1 or more is present.

10.1.2.4. Unsolicited adverse events

Unsolicited adverse event summaries are including serious adverse events unless specified otherwise.

Missing severity, relationship with study vaccine, and outcome of unsolicited adverse events will not be replaced and will appear as 'UNKNOWN' in all statistical output.

10.1.3. Data derivation

10.1.3.1. Age at vaccination in days

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

Age = date of vaccination minus date of birth

10.1.3.2. Age at vaccination in months

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

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

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

10.1.3.3. Age at vaccination in years

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

DOB = 10SEP1983, Date of vaccination = 09SEP2018 -> Age = 34 years

DOB = 10SEP1983, Date of vaccination = 10SEP2018 -> Age = 35 years

10.1.3.4. Weight

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

Weight in kilograms = Weight in pounds / 2.2

10.1.3.5. Height

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

Height in centimeters = Height in inches x 2.54

10.1.3.6. Body mass index (BMI)

BMI will be calculated as follows:

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

10.1.3.7. Temperature

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

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

10.1.3.8. Numerical serology results

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

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

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

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

10.1.3.10. Onset day

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

10.1.3.11. Duration of events

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

10.1.3.12. Counting rules for combining solicited and unsolicited adverse events

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

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

10.1.3.13. Counting rules for occurrences of solicited adverse events

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

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with:

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

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

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

10.1.4.2. Differences in percentages

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

10.1.4.3. Demographic/baseline characteristics statistics

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

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

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

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

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

10.1.4.4. Serological summary statistics

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

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

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

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

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

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

10.1.5.2. Standardized asymptotic confidence intervals around differences in proportions

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

10.2. TFL TOC

The Tables Figures and Listings (TFL) Table of Contents (TOC) which itemizes the planned list of TFL and their associated lay-out is developed as a separate document.

10.3. Glossary of terms

End of Study (EoS) **(Synonym of End of Trial)**	For studies with collection of human biological samples and/or imaging data, the EoS is defined as Last subject last visit (T10). or Last testing results released of samples collected at Visit 6* * In this case EoS must be achieved no later than 8 months after LSLV.
Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.
Responder-based vaccine effectiveness:	The enc-hSBA methodology involves testing the serum samples from each individual subject against a subset of around 35 strains randomly chosen from the overall panel of 110 meningococcus B US strains. Responder-based vaccine effectiveness is assessed based on the percentage of subjects considered responders, i.e., subjects whose serum kills the majority (≥70% in this study) of the tested strains following vaccination.
Test-based vaccine effectiveness:	The enc-hSBA methodology involves testing the serum samples from each individual subject against a subset of around 35 strains randomly chosen from the overall panel of 110 meningococcus B US strains. Test-based vaccine effectiveness is assessed based on the overall percent of individual positive tests following vaccination and represents the reduction in risk compared to the placebo.

11. REFERENCES

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Statistical Analysis Plan	
Detailed Title:	A phase III, randomized, controlled, observer-blind study to demonstrate effectiveness, immunogenicity and safety of GSK's meningococcal Group B and combined ABCWY vaccines when administered to healthy adolescents and young adults.
eTrack study number and Abbreviated Title	205416 [MENB REC 2ND GEN-038 (V72_72)]
Scope:	All data pertaining to the above study
Date of Statistical Analysis Plan	Amendment 6 Final: 27 Feb 2023

APP 9000058193 Statistical Analysis Plan Template V4 (Effective date: 3June2019)

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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
Eli Type	Internal database code for type of elimination code
ELISA	Enzyme-linked immunosorbent assay
EOS	End of Study
ES	Exposed Set
FAS	Full Analysis Set
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titre
GSK	GlaxoSmithKline
LL	Lower Limit of the confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
PCD	Primary completion Date
PPS	Per-Protocol Set
RR	Relative Risk
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
TFL	Tables Figures and Listings
TOC	Table of Contents

1. DOCUMENT HISTORY

Date	Description	Protocol Version
25 Jul 2019	First version	Amendment 1: 23 MAY 2019
15 Jun 2020	Amendment 1	Amendment 2: 18 MAR 2020
25 Mar 2022	Amendment 2	Amendment 4: 12 MAY 2021
25 Apr 2022	Amendment 3	Amendment 4: 12 MAY 2021
08 Sep 2022	Amendment 4	Amendment 4: 12 MAY 2021
12 Jan 2023	Amendment 5	Amendment 4: 12 MAY 2021
27 Feb 2023	Amendment 6	Amendment 4: 12 MAY 2021

2. OBJECTIVES/ENDPOINTS

Table 1 Study objectives and endpoints

Objectives	Endpoints
Primary	
Vaccine effectiveness (Test-based): rMenB+OMV NZ To demonstrate the effectiveness of the rMenB+OMV NZ vaccine against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity using enc-hSBA at 1 month after the 3-dose (0,2,6-months) and 2-dose (0,6-months; 0,2-months) vaccination series when compared to 1 month after the MenACWY vaccination. *Criterion* *Lower limit (LL) of the two-sided 97.5% confidence interval (CI) for vaccine effectiveness is above 65% against a randomly selected strain panel between the:* • *MenB_0_2_6 and ACWY groups (for 0,2,6-months schedule)* • *MenB_0_6 and ACWY groups (for 0,6-months schedule),* • *MenB_0_2_6 and ACWY groups (for 0,2-months schedule)*	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at 1 month after the: • 3-dose vaccination series in MenB_0_2_6 group (Day 211, Month 7) • 2-dose vaccination series in MenB_0_6 group (Day 211, Month 7), and • 2-dose vaccination series in MenB_0_2_6 group (Day 91, Month 3) • 1 month after the MenACWY vaccination in ACWY group (Day 31, Month 1).
Effectiveness (Responder-based): rMenB+OMV NZ To demonstrate the effectiveness of the rMenB+OMV NZ vaccine by assessing the percentages of subjects whose sera kill ≥70% of strains tested using enc-hSBA at 1 month after the 3-dose (0,2,6-months) and 2-dose (0,6-months; 0,2-months) vaccination series of the rMenB+OMV NZ. *Criterion:* *LL of the two-sided 97.5% CI for the percentages of subjects whose sera kill ≥70% of strains is above 65%, tested for:* • *MenB_0_2_6 group (for 0,2,6-months schedule)* • *MenB_0_6 group (for 0,6-months schedule),* • *MenB_0_2_6 group (for 0,2-months schedule)*	The percentages of subjects whose sera kill ≥70% of the strains tested using enc-hSBA, at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group), • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group)

Objectives	Endpoints
The 3 vaccine schedules will be tested for both, test-based and responder-based, in a hierarchical way (starting from 0-2-6, to 0-6 and 0-2). Refer to Protocol Section 10.1 for details on continuing the evaluation.	
Lot-to-lot consistency: MenABCWY vaccine To demonstrate lot-to-lot consistency of the immune responses of 3 lots of the MenACWY component of the MenABCWY vaccine, as measured by hSBA GMTs directed against serogroups A, C, W and Y at 1 month after last vaccination (0,6-months). *Criterion:* *The two-sided 97.5% CIs^ for the ratio of hSBA GMTs of antibodies against serogroups A, C, W and Y are within the [0.5;2.0] equivalence interval for each pair of lots.*	GMTs directed against serogroups A, C, W and Y for each lot (ABCWY-1 group, ABCWY-2 group, ABCWY-3 group) at 1 month after the last vaccination (Day 211, Month 7)
Immunological non-inferiority: MenABCWY vaccine vs. MenACWY vaccine To demonstrate the immunological non-inferiority of the MenABCWY vaccine compared to the MenACWY vaccine as measured by the percentages of subjects achieving a 4-fold rise in hSBA titres against *N. meningitidis* serogroups A, C, W and Y at 1 month after the last MenABCWY vaccination (0,6-months) and 1 month after the MenACWY vaccination. *Criterion:* *LL of the 2-sided 97.5% CI^ for the group difference in percentages of subjects achieving a 4-fold rise* in hSBA titres is above -10%.*	The percentages of subjects with 4-fold rise* in hSBA titres against *N. meningitidis* serogroups A, C, W and Y at 1 month after the: • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • 1 month after the MenACWY vaccination for the ACWY group (Day 31, Month 1) relative to baseline (Day 1, Month 0).
Vaccine effectiveness (Test-based): MenABCWY vaccine To demonstrate the effectiveness of the MenABCWY vaccine against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains as measured by enc-hSBA at 1 month after the last MenABCWY vaccination (0,6-months) when compared to 1 month after the MenACWY vaccination. *Criterion:* *LL of the two-sided 97.5% CI^ for vaccine effectiveness is above 65% against a randomly selected strain panel between the ABCWY group (pooled lots) and the ACWY group.*	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at 1 month after the: • last vaccination for the ABCWY group (pooled) (Day 211, Month 7), and • 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1).
Effectiveness non-inferiority: MenABCWY vaccine vs. rMenB+OMV NZ vaccine To demonstrate the non-inferiority of the effectiveness of the MenABCWY vaccine (0,6-months schedule) compared to the rMenB+OMV NZ vaccine (0,2,6-months or 0,6-months or 0,2-months)† in terms of percentage of samples with bactericidal serum activity using enc-hSBA against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains. *Criterion:*	The percentages of samples with bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains at 1 month after the: • last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • 3-dose vaccination series of rMenB+OMV vaccine (Day 211, Month 7 in MenB_0_2_6 group) or 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) or 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group)†

Objectives	Endpoints
LL of the two-sided 97.5% CI^ for the difference in percentages of samples with bactericidal serum activity using enc-hSBA against a randomly selected panel of endemic US N. meningitidis serogroup B invasive disease strains is above -5% at 1 month after: • *the last vaccination in ABCWY group (pooled lots) (for 0,6 months schedule), and* • *The last vaccination in MenB_0_2_6 group (for 0,2,6-months schedule) or the last vaccination in MenB_0_6 group (for 0,6-months schedule) or the second vaccination in MenB_0_2_6 group (for 0,2-months schedule*	
Effectiveness (Responder-based): MenABCWY vaccine To demonstrate the effectiveness of MenABCWY vaccine by assessing the percentages of subjects whose sera kill ≥70% of strains tested using enc-hSBA at 1 month after the last vaccination of MenABCWY (0,6-months). *Criterion:* *LL of the two-sided 97.5% CI^ for the percentages of subjects whose sera kill ≥70% of strains tested for MenABCWY is above 65%.*	The percentages of subjects whose sera kill ≥70% of the strains tested using enc-hSBA, at 1 month after the last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7).
Safety To evaluate the safety and reactogenicity of the MenB, MenABCWY, and the MenACWY vaccines	• The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [body temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) adverse events (AEs) during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. • The frequencies and percentages of subjects with any unsolicited AEs (including all SAEs, AEs leading to withdrawal, AESIs and medically attended AEs) during the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. • The percentages of subjects with SAEs, AEs leading to withdrawal, AESIs and medically attended AEs throughout the study period [Month 0 to Month 18].
Secondary	
To demonstrate the immunological non-inferiority of the MenABCWY vaccine compared to the rMenB+OMV NZ vaccine as measured by the percentages of subjects achieving a 4-fold rise in hSBA titres against *N. meningitidis* serogroup B indicator strains at 1 month after the last MenABCWY vaccination (0,6-months schedule) and 1 month after the rMenB+OMV NZ vaccination (0,2,6-months or 0,6-months or 0,2-months)†	The percentages of subjects with 4-fold rise** in hSBA titres against *N. meningitidis* serogroup B indicator strains at 1 month after the: • last MenABCWY vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • 3-dose vaccination series of rMenB+OMV vaccine(Day 211, Month 7 in MenB_0_2_6 group) or 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) or 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group)†

Objectives	Endpoints
Criterion: *Non-inferiority will be demonstrated if the LL of the 2-sided 95% CI for the group difference in percentage of subjects achieving a 4-fold rise** in hSBA titres against N. meningitidis serogroup B indicator strains is above -10%.*	relative to baseline (Day 1, Month 0).
To assess the effectiveness of the rMenB+OMV NZ and MenABCWY vaccines against each of the randomly selected endemic US *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series when compared to 1 month after the MenACWY vaccination.	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group) • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • MenACWY vaccination (Day 31, Month 1 in ACWY group).
To describe the distribution of subjects by percentages of serogroup B invasive disease strains killed using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series of rMenB+OMV NZ and MenABCWY vaccines.	The percentages of serogroup B invasive disease strains killed using enc-hSBA in each subject at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7)
To assess the immune response to the rMenB+OMV NZ (0,2,6-months, 0,6-months and 0,2-months) and MenABCWY (0,6-months) vaccines against *N. meningitidis* serogroup B indicator strains at pre-vaccination (Day 1, Month 0) and at 1 month after the last MenABCWY vaccination and at 1 month after the second and third vaccination of rMenB+OMV NZ.	The immune response to the rMenB+OMV NZ and ABCWY vaccines will be evaluated by measuring bactericidal activity against *N. meningitidis* serogroup B indicator strains as following: *1. The percentages of subjects with hSBA titres ≥ lower limit of quantitation (LLOQ) for each (individual response) and all (composite response) serogroup B indicator strains at baseline (Day 1, Month 0) and at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *2. The percentages of subjects with 4-fold rise** in hSBA titres at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group)

Objectives	Endpoints
	• 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 90, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *relative to baseline (Day 1, Month 0).* *3. hSBA GMTs at baseline (Day 1, Month 0) and at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *4. hSBA GMRs at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *relative to the baseline (Day 1, Month 0).*
To assess the immune response to MenABCWY (0,6-months schedule) and MenACWY (single dose) vaccines against *N. meningitidis* serogroups A, C, W and Y, at pre-vaccination (Day 1, Month 0) and at 1 month after the first and the last MenABCWY vaccination and 1 month after the MenACWY vaccination.	*1. The percentage of subjects with hSBA titres ≥ LLOQ for serogroups A, C, W and Y at baseline (Day 1, Month 0) and:* • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1). *2. The percentage of subjects with 4-fold rise* in hSBA titres at 1 month after the:* • first vaccination (Day 31, Month 1) for the ABCWY group (pooled lots) compared to the MenACWY vaccination in the ACWY group (Day 31, Month 1) *relative to baseline (Day 1, Month 0).* *3. hSBA GMTs against N. meningitidis serogroups A, C, W and Y* at baseline (Day 1, Month 0) and: • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1). *4.hSBA GMRs against N. meningitidis serogroups A, C, W and Y at:* • 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7)

Objectives	Endpoints
	for the ABCWY group (pooled lots) as compared to baseline (Day 1, Month 0), and • 1 month after the single MenACWY vaccination in the ACWY group (Day 31, Month 1) as compared to baseline (Day 1, Month 0). *5.The total IgG as measured by ELISA GMCs against serogroups A, C, W and Y* at baseline (Day 1, Month 0) and*:* • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1).

Abbreviations: ELISA = enzyme-linked immunosorbent assay; Enc-hSBA = endogenous complement human serum bactericidal assay; GMC = geometric mean concentrations; GMT = geometric mean titre; GMR = geometric mean ratio; CI = confidence interval; hSBA = human serum bactericidal assay; LOD: limit of detection; LLOQ = lower limit of quantitation; LL = lower limit; AE = Adverse event; SAE = Serious adverse event; AESI = Adverse event of special interest

N.meningitidis serogroup B indicator strains = M14459, 96217, M07-0241084 and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively. The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented either in a protocol amendment or in the clinical report.

Refer to Protocol Section 10 for details on evaluation of objectives and sample size justification. Refer to Glossary of terms for definitions of test-based and responder-based effectiveness

^ If the co-primary effectiveness objectives for rMenB+OMV NZ are met, then all objectives for MenABCWY will be evaluated at 95% CI. Refer to Protocol Section 10.1 for details

P† PIf all objectives of rMenB+OMV NZ are met, the comparator will be the 0,2-months schedule. If the 0,2-months objective is not met, and the 0,6-months is met, then the 0,6-months schedule will be the comparator. If the 0,6-months is also not met, then the 0,2,6-months schedule will be the comparator.

*For the Men A, C, W, Y evaluation, the 4-fold rise is defined as:

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

**For the MenB evaluation, the 4-fold rise per each indicator strain is defined as:

- a post-vaccination‡ hSBA titre ≥4 times the LOD for subjects with a pre-vaccination hSBA titre <LOD
- a post-vaccination‡ hSBA titre ≥4 times the LLOQ for subjects with a pre-vaccination hSBA titre ≥LOD and <LLOQ, and
- a post-vaccination‡ hSBA titre ≥4 times the pre-vaccination hSBA titre for subjects with a pre-vaccination hsBA titre ≥LLOQ

‡ = post-2nd vaccination for 0,6 and 0,2 schedule and post-3rd vaccination for 0,2,6 schedule.

3. STUDY DESIGN

3.1. Scientific rationale for study design

As the rMenB+OMV NZ licensure in the US was issued through accelerated approval, the FDA has requested to demonstrate the effectiveness of the vaccine against an extended panel of serogroup B meningococcal strains (MenB) as a post-marketing commitment in US adolescents and young adults, thus confirming that the vaccine can protect against diverse meningococcal B strains prevalent in the United States.

The availability of a pentavalent meningococcal vaccine in a single administration would however reduce the number of injections and could increase coverage for meningococcal disease caused by *N. meningitidis* serogroups A, B, C, W, and Y worldwide. GSK's investigational MenABCWY combination vaccine is intended to protect against 5 of the most prevalent serogroups of *Neisseria meningitidis* (A, B, C, W, Y) in humans.

Hence, along with the licensed MenB vaccine (*Bexsero*), this Phase III study will also assess the safety, effectiveness, and immunogenicity of the investigational MenABCWY vaccine.

Rationale for effectiveness assessment

As mentioned above, one of the primary purposes of this study is to evaluate the effectiveness of 2 or 3 doses of rMenB+OMV NZ and of 2 doses of the MenABCWY vaccines in healthy adolescents and young adults by measuring the bactericidal activity against 110 endemic US *N. meningitidis* serogroup B strains using an endogenous complement human Serum Bactericidal Assay (enc-hSBA). Sera from the ACWY group receiving the MenACWY vaccine will also be tested against serogroup B meningococcal strains by enc-hSBA as a control for test-based effectiveness assessment. The overall vaccine effectiveness (VE) against all 110 strains combined will be computed by means of a generalised linear model. For additional details see statistical analysis section of the Clinical Study Protocol (Protocol Section 10).

Rationale for lot-to-lot consistency assessment

MenABCWY is a reconstituted vaccine with the lyophilised 'ACWY component' and liquid rMenB+OMV NZ. The MenB component has the same formulation as the commercial *Bexsero*. To demonstrate that the lots of the investigational MenABCWY vaccine are adequately representative of the formulation intended for marketing, equivalence will be assessed for 3 different lots of the ACWY component of the ABCWY vaccine.

Rationale for non-inferiority assessment of MenABCWY vs MenACWY and rMenB+OMV NZ

The study aims to also demonstrate that the investigational combination MenABCWY vaccine is not inferior to a licensed MenACWY vaccine (*Menveo*) and a licensed MenB vaccine (*Bexsero*) which are part of the current standards of care in the US for prevention of invasive disease caused by *N. meningitidis* serogroups A, C, W, Y and by *N. meningitidis* serogroup B, respectively.

Rationale for blood volume collected:

In order to provide the necessary serum volume for the bactericidal assays (enc-hSBA and/ or hSBA(s)), 25 mL whole blood will be collected at Visit 2, Visit 4 and Visit 6. At pre-vaccination (Visit 1), 20 mL whole blood will be collected to provide the necessary serum volume for the hSBA.

Blood samples are taken from all subjects irrespective of the testing status in order to maintain the study blind. Refer to Protocol Section 8.4.2.1 for further details.

Rationale for the selected vaccination schedules

rMenB+OMV NZ: This study aims at demonstrating the VE of the rMenB+OMV NZ vaccine administered as 2-dose vaccine, either with a shorter interval (0,2-months) or a prolonged interval (0,6-months) between doses. A 3-dose schedule has been also added to better characterise the VE.

Note: The rMenB+OMV NZ in the ACWY group is administered in a 0,1-months schedule. This interval is within the recommendations in the summary of product characteristics of *Bexsero* and helps in maintaining the blind. No objectives are associated with this schedule of rMenB+OMV NZ.

MenABCWY: A number of different vaccine formulations were evaluated in MenABCWY Phase I and II clinical studies. The formulation with the same active ingredient composition as the rMenB+OMV NZ (*Bexsero*) and MenACWY (*Menveo*) vaccines was chosen as the final formulation of the investigational MenABCWY vaccine. Two doses administered 6 months apart (0,6-months) is considered the optimal dosing schedule, based on serogroup B immunogenicity results from MenABCWY Phase II clinical studies.

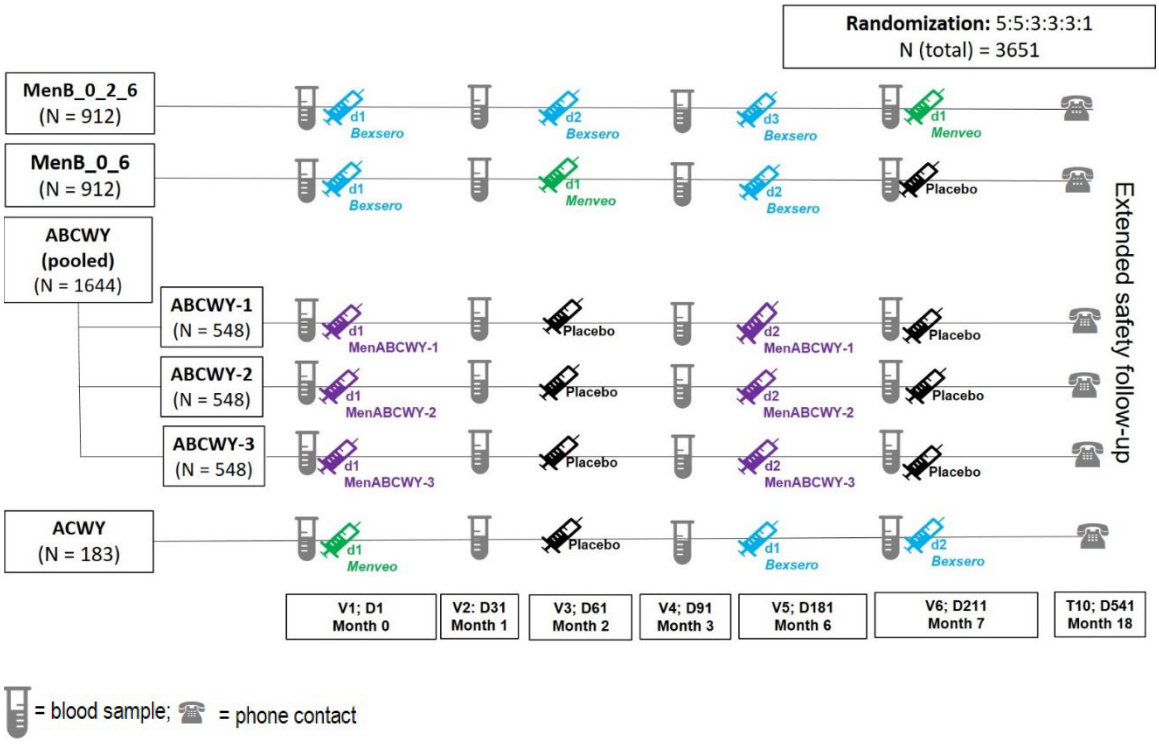
MenACWY: As a comparator for serogroup A, C, W, and Y vaccine effectiveness and immune responses, a single dose of MenACWY vaccine is administered to subjects in the ACWY group. To conform with the standard of care (also in alignment with current ACIP routine immunisation recommendations in US), subjects in the MenB_0_2_6 and MenB_0_6 groups will also receive a dose of MenACWY at Day 211 and Day 61, respectively.

3.1.1. Rationale for the use of placebo

For this study, a placebo (saline solution) will be administered as presented in Figure 1. A placebo is the only available option to minimize possible introduction of reporting bias in collecting information about AEs and to ensure the same number of vaccinations are administered to subjects assigned to either of the six study groups.

3.2. Overall design

Figure 1 Study design overview



N = number of subjects; d = dose; V = visit; D = day; T=Telephone call
Refer to Protocol Table 3 for details on all visits
Note: Home visits may be performed only by sites authorised (as per local regulations and sponsor agreement), with approved site level standard operating procedures (SOP) provided that the compliance with protocol procedures are ensured.

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the schedule of activities (Protocol Section 2), are essential and required for study conduct.

- Type of study: self-contained

- Experimental design: This is a phase III, randomised, controlled, observer-blind, multi-center study to evaluate effectiveness, immunogenicity and safety of rMenB+OMV NZ and MenABCWY vaccines. A total of 3651 healthy adolescents and young adults aged 10-25 years will be enrolled and randomised (5:5:3:3:3:1 ratio) to one of the six parallel study groups:

  – **MenB_0_2_6 group***: subjects will receive 3 doses of rMenB+OMV NZ at Day 1, Day 61 and Day 181 (0, 2 and 0,2,6-months schedule). These subjects will receive 1 dose of the MenACWY vaccine at Day 211**.

  – **MenB_0_6 group**: subjects will receive 2 doses of rMenB+OMV NZ at Day 1 and Day 181 and 1 dose of MenACWY vaccine at Day 61 (rMenB+OMV NZ, 0,6-months schedule). These subjects will receive 1 dose of placebo at Day 211**.

  – **ABCWY-1**: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 1 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211**.

  – **ABCWY-2**: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 2 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211**.

  – **ABCWY-3**: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 3 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211**.

  – **ACWY group**: subjects will receive 1 dose of MenACWY vaccine at Day 1, 1 dose of placebo at Day 61 and 2 doses of rMenB+OMV NZ at Day 181 and Day 211**.

  * MenB_0_2_6 group will also be evaluated for objectives pertaining to 0,2-months vaccination schedule.

  Note 1: A MenB lot will be used for the pre-filled syringe component of the MenABCWY vaccine.

  Note 2: The groups ABCWY-1, ABCWY-2, ABCWY-3 will be pooled into a single group, ABCWY (pooled lots) (except for analysis of lot to lot consistency).

  ** Note 3: In order to let the subjects in MenB_0_2_6 group receive a dose of MenACWY vaccine and for subjects in ACWY group to receive the second dose of rMenB+OMV NZ in line with the vaccine as standard of care (also in line with the Advisory Committee on Immunization Practices (ACIP) recommendations in the US [ACIP, 2011]), the subjects in these groups will receive a vaccination of MenACWY and rMenB+OMV NZ vaccines, respectively, on Day 211 (Visit 6) after completion of the post-vaccination 3 blood sampling. To maintain the blinding of the study, subjects in the rest of the groups (MenB_0_6, ABCWY-1, ABCWY-2 and ABCWY-3) will receive a dose of Placebo. All these vaccines/ product administered at Day 211 are not associated with any study objectives/ endpoints (Safety assessment

conducted after 1 dose of rMenB+OMV NZ in the ACWY group at Day 181 is to maintain the blind of the study).

- Duration of the study: The study duration is approximately 18 months for each subject.
- Primary completion Date (PCD): T10; Day 541.

Refer to Glossary of terms for the definition of PCD.

- End of Study (EoS): the date of release of the last testing results, to be achieved not later than 8 months after Last Subject Last Visit (LSLV) (LSLV = T10; Day 541). If the completion of testing occurs prior the completion of the LSLV the latter date defines the end of study visit.

Refer to Glossary of terms for the definition of EoS.

- Study groups:

Table 2 Study groups and treatment foreseen in the study

Study Groups	Number of subjects	Age (Min-Max)	Treatment name	Vaccine/Product name
MenB_0_2_6	912	10 – 25 y	*Bexsero* (Injection)	rMenB+OMV NZ
			Menveo (Injection)	MenACWY
MenB_0_6	912		*Bexsero* (Injection)	rMenB+OMV NZ
			Menveo (Injection)	MenACWY
			Placebo (Injection)	NaCl
ABCWY-1	548		MenABCWY (with Lot 1 of ACWY) (Injection)	MenABCWY-1
			Placebo (Injection)	NaCl
ABCWY-2	548		MenABCWY (with Lot 2 of ACWY) (Injection)	MenABCWY-2
			Placebo (Injection)	NaCl
ABCWY-3	548		MenABCWY (with Lot 3 of ACWY) (Injection)	MenABCWY-3
			Placebo (Injection)	NaCl
ACWY	183		*Menveo* (Injection)	MenACWY
			Placebo (Injection)	NaCl
			Bexsero (Injection)	rMenB+OMV NZ

Table 3 Overview of study design: Vaccination and Blood Draw Schedule

Visits **Study Day**	**Visit 1** **Day 1**	Visit 2 Day 31	**Visit** 3 **Day 61**	**Visit** 4 **Day 91**	**Visit** 5 **Day 181**	**Visit** 6 **Day 211**
Group **MenB_0_2_6** **N=912**	Pre-vacc Blood sample rMenB+OMV NZ	Post-vacc 1 Blood sample	rMenB+OMV NZ	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample MenACWY
Group **MenB_0_6** **N=912**	Pre-vacc Blood sample rMenB+OMV NZ	Post-vacc 1 Blood sample	MenACWY	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample Placebo
Group **ABCWY-1** **N=548**	Pre-vacc Blood sample MenABCWY-1	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-1	Post-vacc 3 Blood sample Placebo
Group **ABCWY-2** **N=548**	Pre-vacc Blood sample MenABCWY-2	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-2	Post-vacc 3 Blood sample Placebo
Group **ABCWY-3** **N=548**	Pre-vacc Blood sample MenABCWY-3	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-3	Post-vacc 3 Blood sample Placebo
Group **ACWY** **N=150**	Pre-vacc Blood sample MenACWY	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample rMenB+OMV NZ

N = number of subjects; Pre-vacc = pre-vaccination; Post-vacc = post-vaccination

- Treatment allocation: At Day 1, prior to the study vaccination, subjects will be randomised to 1 of the 6 study groups according to a 5:5:3:3:3:1 ratio.
- Blinding: Observer-blind. Kindly refer to Protocol Section 7.3 for details on blinding and unblinding procedures.
- Sampling schedule:
  - A total of 4 blood samples* will be collected from each subject at Day 1 (pre-vaccination blood sample; approximately 20 mL), at Day 31 (post-vaccination 1 blood sample; approximately 25 mL), at Day 91 (post-vaccination 2 blood sample; approximately 25 mL) and at Day 211 (post-vaccination-3 blood sample; approximately 25 mL).
  - Urine sampling: Urine samples for pregnancy testing will be collected from female subjects of child-bearing potential at Visit 1 (Day 1), Visit 3 (Day 61), Visit 5 (Day 181) and Visit 6 (Day 211) prior to the vaccination.

  * Insufficient blood volume may lead to test cancellation and jeopardise the statistical power. Hence, every effort must be done to collect blood volume as per protocol requirements.
- Data collection: standardised Electronic Case Report Form (eCRF). Solicited symptoms will be collected using a subject Diary (electronic Diary [eDiary]).
- Safety monitoring: Regular safety follow-up will be done through telephone calls (T). There will also be an extended safety follow-up (ESFU) phone call 12 months post-vaccination 3 (Day 181; Visit 5). This ESFU phone call will also mark the study conclusion. Refer to Protocol Table 3 and Protocol Section 8.5.3 for details on the safety follow-up.

3.3. Number of subjects

A total of 3651 subjects will be randomised in a ratio of 5:5:3:3:3:1; 912 each in MenB_0_2_6 and MenB_0_6 groups, 548 in each ABCWY groups and 183 in ACWY group. Assuming a 25% drop out rate, this should provide approximately 684 evaluable subjects in each of the MenB groups, 411 evaluable subjects in each of the ABCWY groups and 137 evaluable subjects in the ACWY group.

Refer to Protocol Section 10.1 for a detailed description of the criteria used in the determination of sample size.

Withdrawals will not be replaced.

3.4. Subject and study completion

A subject is considered to have completed the study, if the subject is available for the concluding contact (T10; Day 541) as described in the protocol.

Global completion of the study is required in order to provide enough subjects as defined in Protocol Section 10.1 Sample Size Determination.

4. ANALYSIS SETS

4.1. Definition

For purposes of analysis, the following analysis sets are defined:

4.1.1. Enrolled Set

Subject/ Subject for whom parent(s)/LAR's agreed to participate in a clinical study after completion of the informed consent process, who meet screening/eligibility criteria and randomized and/or received study intervention or undergone an invasive procedure.

4.1.2. Exposed Set

All subjects who received at least 1 dose of the study treatment. The allocation in a group is done in function of all administered treatments.

4.1.3. Full Analysis Set

All subjects who received at least 1 dose of the study treatment and have post-vaccination effectiveness or immunogenicity data.

4.1.4. Per Protocol Set

All subjects in the Full Analysis Set minus subjects with protocol deviations that lead to exclusion from the Per Protocol Set.

4.1.5. Solicited Safety Set

All subjects who received at least 1 dose of the study treatment (Exposed Set) who have solicited safety data beyond 30 minutes post vaccination.

4.1.6. Unsolicited Safety Set

All subjects who received at least 1 dose of the study treatment (Exposed Set) that report unsolicited AEs/report not having unsolicited AEs.

4.1.7. Overall Safety Set

All subjects that belong to the Unsolicited safety or/and to the Solicited safety set.

4.2. Criteria for eliminating data from Analysis Sets

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

4.2.1. Elimination from Exposed Set (ES)

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

4.2.2. Elimination from Per protocol Set (PPS)

4.2.2.1. Excluded subjects

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

Table 4 Elimination code and condition to exclude a subject from the PPS analysis

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
800	Fraudulent data	All	All
900	Invalid informed consent	All	All
1030	Study vaccine not administered at all	All	All
1050	Randomization failure	Visit 1, 3, 5	All
1060	Randomization code was broken	All	All
1070.1	Subjects got vaccinated with the correct vaccine but containing a lower volume	Visit 1, 3, 5	All
1070.2	Vaccination not according to protocol	Visit 1, 3, 5	All
1080	Vaccine temperature deviation	Visit 1, 3, 5	All
1090	Expired vaccine administered	Visit 1, 3, 5	All
1500.1	Other deviation from study procedures not able to classified under any other categories	All	All
1500.2	Any other GCP non-compliance not able to classified under any other categories	All	All
2010	Protocol violation (inclusion/exclusion criteria)	All	All
2040	Administration of any medication forbidden by the protocol	Visit 1, 3, 5	All
2050	Not withdrawn after developing withdrawal criteria other than prohibited concomitant vaccination/medication (medical condition forbidden)	All	All
2060	Concomitant infection related to the vaccine which may influence immune response (only meningococcal infection)	All	All
2080	Subjects did not comply with vaccination schedule	Visit 3, 5	All

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
2090	Subjects did not comply with blood sample schedule	Visit 2, 4, 6	All
2100	Serological results not available post-vaccination for all tests	Visit 2, 4, 6	All
2120	Obvious incoherence or abnormality or error in data related to testing	Visit 2, 4, 6	All
2130	Biological sample specimen procedures not compliant with protocol	Visit 2, 4, 6	All

4.2.3. Elimination from unsolicited and solicited safety set

4.2.3.1. Excluded subjects

4.2.3.1.1. Unsolicited safety set

Code 1030 (Study vaccine not administered at all), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1150 (no post-vaccination safety data) will be used for identifying subjects eliminated from the unsolicited safety set.

4.2.3.1.2. Solicited safety set

Code 1030 (Study vaccine not administered at all), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1160 (no post-vaccination solicited safety data) will be used for identifying subjects eliminated from the solicited safety set.

5. STATISTICAL ANALYSES

Standard data derivation rules and statistical methods are described in section 10.1 while the study specific data derivation rules and stat methods are described in section 9.

5.1. Disposition of subjects

5.1.1. Analysis of disposition of subjects planned in the protocol

Number of subjects enrolled, vaccinated subjects (at least 1 vaccination, full vaccination course), reason for early withdrawal, FAS, and PPS will be described by vaccine group.

5.1.2. Additional considerations

Not applicable

5.2. Demography and baseline characteristics analyses

5.2.1. Analysis of demography and baseline characteristics planned in the protocol

Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age, height, weight, and body mass index (BMI) at enrolment will be calculated overall and by vaccine group.

Distributions of subjects by sex, race, ethnic origin will be summarised overall and by vaccine group.

5.2.2. Additional considerations

A summary table of important protocol deviations related to COVID-19 will be provided. Also, a listing will be produced.

5.3. Primary effectiveness and immunogenicity

5.3.1. Analysis of primary effectiveness and immunogenicity planned in the protocol

Refer to Glossary of terms for definitions of test-based and responder-based vaccine effectiveness. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then all objectives for MenABCWY will be evaluated at 95% CI (Sections 5.3.1.7 through 5.3.1.11, ref Protocol Section 10.1).

5.3.1.1. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Analysis set: Per-protocol set (PPS) will be the primary analysis population

Statistical method: The VE is defined as 1- RR= (1- percentage of samples without bactericidal serum activity at 1:4 dilution in MenB group / percentage of samples without bactericidal serum activity at 1:4 dilution in the ACWY group) x100% and it will be analyzed using a generalised linear model with vaccine group, strain, and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) as independent variables. Furthermore, a repeated statement will be used to estimate the variance of the RR including correlation within subject's responses to different strains. If the statistical model does not converge due to (one of) the factor(s), a model without this/these factor(s) will be fitted instead. The response variable of the model will be the Bernoulli distributed outcome without bactericidal activity at a 1:4 dilution (i.e. response is 1 if titre < 4, and 0 if titre ≥ 4), at 1 month after the last vaccination (Month 7) in the MenB group and at Month 1 for the ACWY group. Each subject will contribute with approximately 35 measures to this analysis, each of the measures corresponding to the response variable to one of the 35 strains randomly assigned to be tested with the samples available for that specific subject.

In order to obtain the VE measure which is a measure based on the relative risk (RR), a generalised linear model will be used with the Binary distribution and link function log in order to compute the log RR and the corresponding 97.5% CI. The obtained values will be exponentiated to obtain the RR and the corresponding 97.5% CI. The VE will be computed as 100% x (1 – RR). Effectiveness of rMenB+OMV NZ (0,2,6-months schedule) will be demonstrated if the lower limit of the two-sided 97.5% CI for VE between MenB and the ACWY group is above 65%.

5.3.1.2. Effectiveness (Responder-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Analysis set: FAS will be the primary analysis population.

Statistical method: The percentage of responders (see definition in Glossary of terms) and the corresponding exact two-sided 97.5% CI based on Clopper-Pearson method will be calculated [Clopper, 1934].

The objective is to demonstrate that the lower limit of the 97.5% CI for the percentage of responders is higher than 65%.

5.3.1.3. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 5.3.1.1

5.3.1.4. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 5.3.1.2

5.3.1.5. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 5.3.1.1

5.3.1.6. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 5.3.1.2

5.3.1.7. Lot-to-lot consistency: MenABCWY - ACWY component

Analysis set: The analysis of lot-to-lot consistency will be based on the PPS.

Statistical method: For each of the three ABCWY lots (Lots 1, 2 and 3 of the MenACWY component of the ABCWY vaccine), GMTs and 97.5% CIs will be calculated by exponentiating (base 10) the least squares means and the lower and upper limits of the 97.5% CIs of the log transformed titres (base10) obtained from an Analysis of Variance

(ANOVA) with factors for vaccine lot and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)). Additionally, lot-to-lot GMT ratios will be computed for each pair of ABCWY lots. Ninety-seven point five percent (97.5%) CIs for the ratios of GMTs will be constructed by exponentiating the difference of the least square means of the log transformed titres and the lower and upper limits of the 97.5% CIs on the difference obtained from the ANOVA model above.

Lot-to-lot consistency criterion: The three ABCWY lots will be considered equivalent if for each of the 4 serogroups A, C, W and Y and each pair of vaccine lots, the two-sided 97.5% CI on the ratio of GMTs at 1 month after the last vaccination will be contained within the interval [0.5, 2.0].

If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.1.8. Immunological non-inferiority: MenABCWY vs. MenACWY

Analysis set: PPS restricted to subjects without previous ACWY vaccination will be the primary analysis population.

Statistical method: The percentage of subjects with 4-fold riseP*P in hSBA titres against MenACWY indicator strains A, C, W and Y and the corresponding exact two-sided 97.5% CIs based on Clopper-Pearson method will be calculated for the ABCWY (pooled lots) group and the ACWY group [Clopper, 1934]. The 97.5% CIs for the difference in percentages between ABCWY (pooled lots) and ACWY group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-Inferiority criterion: Non-inferiority of MenABCWY vaccine for the proportion of subjects with 4-fold rise will be demonstrated if the lower limit of the two-sided 97.5% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY (pooled) lots –ACWY) is above -10%.

* For the Men A, C, W, Y evaluation, the 4-fold rise is defined as:

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

Table 5 reads the LOD and LLOQ of MenACWY indicator strains used in the definition of 4-fold rise provided by the laboratory.

Table 5 LOD, LLOQ, and ULOQ of MenACWY indicator strains

Strain	LOD	LLOQ	ULOQ
Men A (3125)	CCI [redacted]		
Men C (C11)			
Men W (240070)			
Men Y (860800)			

If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.1.9. Vaccine effectiveness (Test-based): MenABCWY

See Section 5.3.1.1. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the VE for MenABCWY will be evaluated at 95% CI.

5.3.1.10. Effectiveness non-inferiority: MenABCWY vs. rMenB+OMV NZ

Analysis set: PPS will be the primary analysis population.

Statistical method: The percentage of samples with bactericidal activity measured by enc-hSBA at 1:4 dilution and the corresponding exact two-sided 97.5% CIs based on Clopper-Pearson method will be calculated for the ABCWY (pooled lots) group and the MenB group comparator that will be selected (ref: the footnote of Figure 2). The 97.5% CIs for the difference in percentages between ABCWY (pooled lots) and selected MenB group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-Inferiority criterion: Non-inferiority of MenABCWY vaccine for the percentage of samples with bactericidal activity measured by enc-hSBA at 1:4 dilution will be demonstrated if the lower limit of the two-sided 97.5% CI for the difference between the 2 groups (ABCWY (pooled) lots – MenB) is above -5%.

If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.1.11. Effectiveness (Responder-based): MenABCWY

See Section 5.3.1.2. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the effectiveness (responder-based) for MenABCWY will be evaluated at 95% CI.

5.3.2. Additional considerations

Analyses of the primary effectiveness and immunogenicity objectives will be repeated by age group (10-17 years of age and 18-25 years of age), race, sex, region (US/ ex-US), and subjects with and without a previous MenACWY vaccination (primed and unprimed).

5.3.2.1. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

The SAS code to analyse the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) objective is specified below. Treatment, region, age category, previous ACWY vaccination, and strains will be modelled as fixed effect. To account for a possible over-dispersion, the DSCALE option in the model statement will be evaluated first. The DSCALE will be kept in the model only if the F-statistics for the DSCALE parameter is significant ($p<0.05$). The following SAS code will be used for the VE calculation:

```
ods trace on;
ods output GEEEmpPEst = genmod_stats
CONVERGENCESTATUS = converge ;

PROC GENMOD data=dataset descending;
class trtgrp strain region agecat previousACWY subject_id ;
model outcome = trtgrp strain region agecat previousACWY / dist= bin
link= log DSCALE;
repeated subject = subject_id / type= CS withinsubject= strain;
estimate 'MenB026-ACWY' trtgrp 1 0 0 0 0 -1/ alpha=0.025 exp;

/*trtgrp R is MenB0,2,6 and trtgrp W is ACWY*/

run;

ods output close;

data genmod_stats;
set genmod_stats;
where parm = 'trtgrp' and level1 = '1';
rr = exp(estimate);
ub = exp(uppercl);
ve = (1 - rr)*100 ;
ve_ll = (1 - ub) * 100 ;
if ve_ll > 65 then success = 1 ;
else success = 0 ;
run;
```

where outcome represents the Bernoulli distributed outcome without bactericidal activity at a 1:4 dilution (i.e. response is 1 if titre < 4, and 0 if titre ≥ 4), one month after the 3rd vaccination in MenB 0,2,6 and one month after the MenACWY vaccination for the ACWY arm, trtgrp indicates the vaccine groups, strain is the serogroup B strain variable, region is either US or ex-US, agecat is the age at enrolment (10-17 YoA or 18-25 YoA), and previousACWY is previous ACWY vaccination (y/n) at enrolment.

rr is the relative risk (RR), which is obtained from the estimated parameters from PROC GENMOD. Vaccine effectiveness (VE) is then derived as (1-rr)x100%.

ub represents the upper bound of the 97.5% CI of the relative risk. ve_ll is the lower bound of the 97.5% CI for VE, if the value is greater than 65%, then the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) objective is successful.

5.3.2.2. Effectiveness (Responder-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Not applicable

5.3.2.3. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 5.3.2.1, with the difference in the treatment arm:

```
PROC GENMOD data=dataset descending;
class trtgrp strain region agecat previousACWY subject_id ;
model outcome = trtgrp strain region agecat previousACWY / dist= bin
link= log DSCALE ;
repeated subject = subject_id / type= CS withinsubject= strain ;
estimate 'MenB06-ACWY' trtgrp 0 1 0 0 0 -1/ alpha=0.025 exp;

/*trtgrp S is MenB0,6 and trtgrp W is ACWY*/

run;
```

5.3.2.4. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

Not applicable

5.3.2.5. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 5.3.2.1, with the difference the outcome data for group R is from one month after the 2nd vaccination instead of one month after the 3rd vaccination.

5.3.2.6. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

Not applicable

5.3.2.7. Lot-to-lot consistency: MenABCWY - ACWY component

Not applicable

5.3.2.8. Immunological non-inferiority: MenABCWY vs. MenACWY

As a sensitivity analysis, a parametric model will be run. A generalized linear model with factors for vaccine group and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA)) will be ran, with the Binary distribution and link function is identity, and outcome is 4-fold rise. If the lower limit of the two-sided 97.5% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY (pooled) lots –ACWY) coming from the model is above -10%, also the sensitivity analysis has demonstrated non-inferiority. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.2.9. Vaccine effectiveness (Test-based): MenABCWY

See Section 5.3.2.1, with the difference in the estimate statement:

```
PROC GENMOD data=dataset descending;
class trtgrp strain region agecat previousACWY subject_id ;
model outcome = trtgrp strain region agecat previousACWY / dist= bin
link= log DSCALE ;
repeated subject = subject_id / type= CS withinsubject= strain ;
estimate ' MenABCWY-ACWY' trtgrp 0 0 1 1 1 -3/ alpha=0.025 exp
divisor=3;

/*trtgrp T, U, and V are the ABCWY-1, ABCWY-2, and ABCWY-3 lots and
trtgrp W is ACWY*/
run;
```

5.3.2.10. Effectiveness non-inferiority: MenABCWY vs. rMenB+OMV NZ

As a sensitivity analysis, a parametric model will be run. A generalized linear model with factors for vaccine group and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) will be ran, with the Binary distribution and link function is identity, and outcome is bactericidal activity measured by enc-hSBA at 1:4 dilution. If the lower limit of the two-sided 97.5% CI for the difference in percentage of samples with bactericidal activity measured by enc-hSBA at 1:4 dilution between the 2 groups (ABCWY (pooled) lots –MenB) coming from the model is above -5%, also the sensitivity analysis has demonstrated non-inferiority. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

In addition to the comparison of MenABCWY vs the selected MenB schedule per Section 5.3.1.10, MenABCWY will be compared to the other MenB schedule/schedules, whichever is applicable in the same way as described in Section 5.3.1.10. If MenB 0,2 schedule is selected as comparator, in addition MenABCWY will be compared to Menb 0,6 and MenB 0,2,6 schedule. If MenB 0,6 schedule is selected as comparator, in addition MenABCWY will be compared to MenB 0,2,6 schedule. No success criterion is defined for these group comparisons.

5.3.2.11. Effectiveness (Responder-based): MenABCWY

Not applicable

5.4. Secondary effectiveness and immunogenicity

5.4.1. Analysis of secondary effectiveness and immunogenicity planned in the protocol

5.4.1.1. Immunological non-inferiority: MenABCWY vs. rMenB+OMV NZ

Analysis set: PPS will be the primary analysis population.

Statistical method: The percentages of subjects with 4-fold rise** in hSBA titres against N. meningitidis serogroup B indicator strains (M14459, 96217, M07-0241084* and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively) at 1 month after the last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) and 1 month after the 3-dose vaccination series (Day 211, Month 7) in MenB_0_2_6 group or 2-dose vaccination series (Day 211, Month 7) in MenB_0_6 group or 2-dose vaccination series (Day 91, Month 3) in MenB_0_2_6 group and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated [Clopper, 1934]. The 95% CIs for the difference in percentages between ABCWY group (pooled lots) and MenB_0_2_6 group and MenB_0_6 group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-inferiority criterion: Non-inferiority of MenABCWY vaccine for the proportion of subjects with 4-fold rise will be demonstrated if the lower limit of the 2-sided 95% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY group (pooled lots) –selected MenB group) is above -10%.

* The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented either in a protocol amendment or in the clinical report.

** For the MenB evaluation, the 4-fold rise per each indicator strain is defined as:

- a post-vaccination‡ hSBA titre ≥4 times the LOD for subjects with a pre-vaccination hSBA titre <LOD
- a post-vaccination‡ hSBA titre ≥4 times the LLOQ for subjects with a pre-vaccination hSBA titre ≥LOD and <LLOQ, and
- a post-vaccination‡ hSBA titre ≥4 times the pre-vaccination hSBA titre for subjects with a pre-vaccination hSBA titre ≥LLOQ

‡ = post-2nd vaccination for 0,6 and 0,2 schedule and post-3rd vaccination for 0,2,6 schedule).

Table 6 reads the LOD and LLOQ of hSBA titres against N. meningitidis serogroup B indicator strains used in the definition of 4-fold rise provided by the laboratory.

Table 6 LOD and LLOQ of hSBA titres against N. meningitidis serogroup B indicator strains

Strain	LOD	LLOQ
NZ98-254	CCI [redacted]	
96217		
M14459		
M13520		

5.4.1.2. Effectiveness by each of the endemic US N. meningitidis serogroup B strains

Analysis set: FAS will be the primary analysis population. The ABCWY (pooled lots) group and the MenB group comparator that will be selected (ref: the footnote of Figure 2) will be used for the purpose of this analysis.

Statistical method: The VE per strain will be calculated as described in Section 5.3.1.1, using a generalised linear model with vaccine group, and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) as independent variables, and alpha=0.05 leading to 95% CI. In case for a strain 100% response will be observed in both vaccine groups, VE against these strain will be assessed by calculating 95% CI for relative risk from raw proportions, and VE=1-RR.

5.4.1.3. Distribution of percentages of serogroup B invasive disease strains killed

Analysis set: FAS will be the primary analysis population. The ABCWY (pooled lots) group and the MenB group comparator that will be selected (ref: the footnote of Figure 2) will be used for the purpose of this analysis.

Statistical method: Summary statistics of the percentage of serogroup B invasive disease strains killed within a subject using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series of rMenB+OMV NZ and MenABCWY vaccines.

Summary statistics and 95% CI for the mean percentage will be presented, as well as a Figure of the cumulative distribution function.

5.4.1.4. Immune response of MenABCWY, rMenB+OMV NZ and MenACWY

Analysis set: The analysis will be based on the FAS.

Statistical method: The hSBA titres at each time point for all groups (ABCWY group (pooled lots), MenB_0_2_6 and MenB_0_6 groups) will be logarithmically transformed (base10) to fulfil the normal distribution assumption. For each N. meningitidis serogroup A, C, W and Y and each B indicator strain (M14459, 96217, M07-0241084* and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively), the GMTs and GMRs (post-vaccination/baseline) will be obtained from an Analysis of Variance (ANOVA) with factors for vaccine group, region (US/ex-US), age category (10-17 YoA/18-25 YoA), and previous MenACWY vaccination (y/n), and then exponentiating the log-transformed means and their 95% CIs. The ratio of GMTs and GMRs between two groups and the corresponding CI will be estimated additionally.

The total IgG (as measured by ECL) against serogroups A, C, W and Y at baseline (Day 1, Month 0) and

- at 1 month after the first (Day 31, Month 1) and the last vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and
- at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1),

will be analyzed in a comparable way as described above for hSBA titres. Since total IgG is measured as concentration instead of titer, the resulting geometric mean of the concentrations is abbreviated as GMC.

Table 7 LLOQ and ULOQ of total IgG (as measured by ECL) MenACWY indicator strains

Strain	LLOQ	ULOQ
Men A	CCI [redacted]	
Men C		
Men W		
Men Y		

For each N. meningitidis A, C, W and Y and for each (individual response) and all (composite response) serogroup B indicator strain (M14459, M07-0241084*, 96217and NZ98/254) the percentages of subjects with hSBA titres ≥LLOQ and of subjects with 4-fold rise and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated for each study group at each timepoint not previously analyzed. Ninety-five percent (95%) CIs for the difference in percentages between ABCWY (pooled lots) on the one hand and MenB_0_2_6, MenB_0_6, and ACWY groups, respectively, on the other hand, will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

* The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented either in a protocol amendment or in the clinical report.

For each N. meningitidis serogroup A, C, W and Y, analyses of hSBA GMTs, percentages of subjects with hSBA titres ≥LLOQ and of subjects with 4-fold rise, will be repeated by subjects with and without a previous MenACWY vaccination (primed and unprimed). Similarly, analyses of GMCs of the total IgG (as measured by ECL) against serogroups A, C, W and Y will be repeated by subjects with and without a previous MenACWY vaccination (primed and unprimed).

5.4.1.5. Cohen kappa level of agreement

The human serum bactericidal assay (hSBA) and the endogenous complement human serum bactericidal assay (enc-hSBA) provide two different types of results for B strains; the hSBA gives a quantitative, continuous result (hSBA titer) while the enc-hSBA gives a qualitative, categorical result (with/without bactericidal activity).

To assess the agreement between hSBA and enc-hSBA, the Kappa statistics [Cohen, 1960] will be used and the hSBA results will be categorized as follows:

- The hSBA will be categorized as <LLOQ and ≥LLOQ (Ref. Table 6). Agreement will be assessed versus the positive and negative categories of the enc-hSBA at 1:4 dilution.

To evaluate the strength of the agreement, the following scale [Landis, 1977] will be used:

Table 8 Strength of agreement scale

Kappa	Strength of Agreement
< 0.00	Poor
0.00-0.20	Slight
0.21-0.40	Fair
0.41-0.60	Moderate
0.61-0.80	Substantial
0.81-1.00	Almost Perfect

A 95% Confidence Interval (CI) will be provided together with the point estimate of the Kappa for each of the above situations. The McNemar test will be also performed using the same categorizations of the hSBA results as described above. The aforementioned comparisons/tests will be all performed overall across vaccine groups, separately for each serogroup B test strain. The following SAS code will be used for the Kappa calculation and the McNemar test:

```
PROC FREQ data=dataset;
table assay1_res*assay2_res / agree;
run;
```

where assay1_res represents the enc-hSBA result, assay2_res represents the precategorized hSBA result.

5.4.2. Additional considerations

5.4.2.1. Immunological non-inferiority: MenABCWY vs. rMenB+OMV NZ

As a sensitivity analysis, a parametric model will be run. A generalized linear model with factors for vaccine group and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) will be ran, with the Binary distribution and link function is identity, and outcome is 4-fold rise. If the lower limit of the two-sided 95% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY (pooled) lots –MenB) coming from the model is above -10%, also the sensitivity analysis has demonstrated non-inferiority.

5.4.2.2. Effectiveness by each of the endemic US N. meningitidis serogroup B strains

The SAS code to analyse the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) by strain is specified below. Treatment, and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) will be modelled as fixed effect. To account for a possible over-dispersion, the DSCALE option in the model statement will be evaluated first. The DSCALE will be kept in the model only if the F-statistics for the DSCALE parameter is significant ($p<0.05$). The following SAS code will be used for the VE calculation:

```
ods trace on;
ods output  GEEEmpPEst = genmod_stats
CONVERGENCESTATUS = converge ;

PROC GENMOD data=dataset descending;
class trtgrp region agecat previousACWY;
by strain ;
model outcome = trtgrp region agecat previousACWY / dist= bin link= log
DSCALE alpha=0.05;
estimate 'MenB026-ACWY' trtgrp 1 0 0 0 0 -1/ alpha= 0.05 exp;

/*trtgrp R is MenB0,2,6 and trtgrp W is ACWY*/

run;

ods output close;

data genmod_stats;
set genmod_stats;
by strain ;
where parm = 'trtgrp' and level1 = '1';
rr = exp(estimate);
ub = exp(uppercl);
ve = (1 - rr)*100 ;
ve_ll = (1 - ub) * 100 ;
if ve_ll > 65 then success = 1 ;
else success = 0 ;
run;
```

where outcome represents the Bernoulli distributed outcome without bactericidal activity at a 1:4 dilution (i.e. response is 1 if titre < 4, and 0 if titre ≥ 4), one month after the 3rd vaccination in MenB0,2,6 and one month after the MenACWY vaccination for the ACWY arm, trtgrp indicates the vaccine groups, strain is the serogroup B strain variable, region is either US or ex-US, agecat is the age at enrolment (10-17 YoA or 18-25 YoA), and previousACWY is previous ACWY vaccination (y/n) at enrolment.

rr is the relative risk (RR), which is obtained from the estimated parameters from PROC GENMOD. Vaccine effectiveness (VE) is then derived as (1-rr)x100%.

ub represents the upper bound of the 95% CI of the relative risk. ve_ll is the lower bound of the 95% CI for VE, if the value is greater than 65%, then the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) objective is successful.

In summary in case of convergence issue the following hierarchical decision tree will be applied

- Binary model including region, agecat, and previousACWY
- Binary model, excluding region, agecat, and previousACWY
- Cochran-Mantel-Haenszel (CMH) method (if strain has 100% killed or 0% killed for ANY treatment)
- VE set to 0% (if strain has 100% killed for both treatment)

5.4.2.3. Distribution of percentages of serogroup B invasive disease strains killed

Not applicable

5.4.2.4. Immune response of MenABCWY, rMenB+OMV NZ and MenACWY

Not applicable

5.5. Safety and reactogenicity

5.5.1. Analysis of safety and reactogenicity planned in the protocol

Distribution of subjects by vaccinations will be summarised by vaccine group for the Enrolled Set. In case of vaccination error, subjects will be analyzed “as treated” (according to the vaccine the subject received).

Analysis sets: Solicited Safety Set (solicited local and systemic adverse events and other solicited adverse events), Unsolicited Safety Set (unsolicited adverse events), and Overall Safety Set.

Endpoint	Statistical Analysis Methods
Primary	**Endpoints description**: The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) adverse events during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. All solicited adverse events will be summarised according to defined severity grading scales, see protocol section 12.5.9.3. Frequencies and percentages of subjects experiencing each adverse event will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic adverse event overall and at each time point will also be presented. Post-vaccination solicited adverse events reported from Day 1 to Day 7 will be summarised for the intervals Day 1-3, Day 4-7, and Day 1-7 by maximal severity and by vaccine group, excluding the 30-minute measurement, which will be summarised separately. The severity of solicited local adverse events, including redness (erythema) at injection site, swelling of skin at injection site, and hardness of skin at injection site will be summarised according to categories based on linear measurement: None (1 to 24mm); Mild (25 to 50mm); Moderate (51 to 100mm); Severe (>100mm). Injection site tenderness and systemic reactions (except fever) occurring up to 7 days after each vaccination at Day 1, Day 61 and Day 181 will be summarised according to "mild", "moderate" or "severe". Each solicited local and systemic adverse event will also be further summarised as "none" versus "any" (for fever the latter will be ≥38.0 °C). Use of antipyretics and analgesics will be summarised by frequency by type of use (prophylactic versus treatment) and percentage of subjects reporting use. Body temperature will be summarised 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 temperatures ≥ 38.0 °C and temperatures ≥ 40.0 °C will also be presented.
	Endpoints description: The frequencies and percentages of subjects with any unsolicited ***AEs*** (including all SAEs), ***AEs*** leading to withdrawal and medically attended ***AEs*** during the 7 and the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. The frequencies and percentages of subjects with SAEs, ***AEs*** leading to withdrawal***, AESIs*** and medically attended ***AEs*** throughout the study period. This analysis applies to all adverse events occurring during the study, judged either as possibly related, or not related to vaccination by the investigator, recorded in AE CRF, with a start date on or after the date of first vaccination. AE starting prior to the first vaccination will only be listed. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class. All reported adverse events, as well as adverse events judged by the investigator as possibly related to study vaccine, will be summarised 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 adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted. Separate summaries will be produced for the following categories: • Serious adverse events. • Adverse events that are possibly related to vaccine. • Adverse events of special interest. • Adverse event leading to withdrawal. • Adverse events leading to a medically attended visit. Data listings of all adverse events will be provided by subject. In addition, adverse events in the categories above will be provided as listed data. Local and systemic AEs will be analyzed by point estimates with associated 95% CIs [Clopper, 1934].

5.5.2. Additional considerations

For analyses of the safety and reactogenicity endpoints, subjects will be analyzed "as treated" according to the actual vaccination a subject received.

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

Analyses of safety objectives will be repeated by age group (10-17 years of age and 18-25 years of age), race, sex, region (US/ ex-US), and with and without a previous MenACWY vaccination (primed and unprimed).

A Table and Listing of COVID-19 AE cases will be provided.

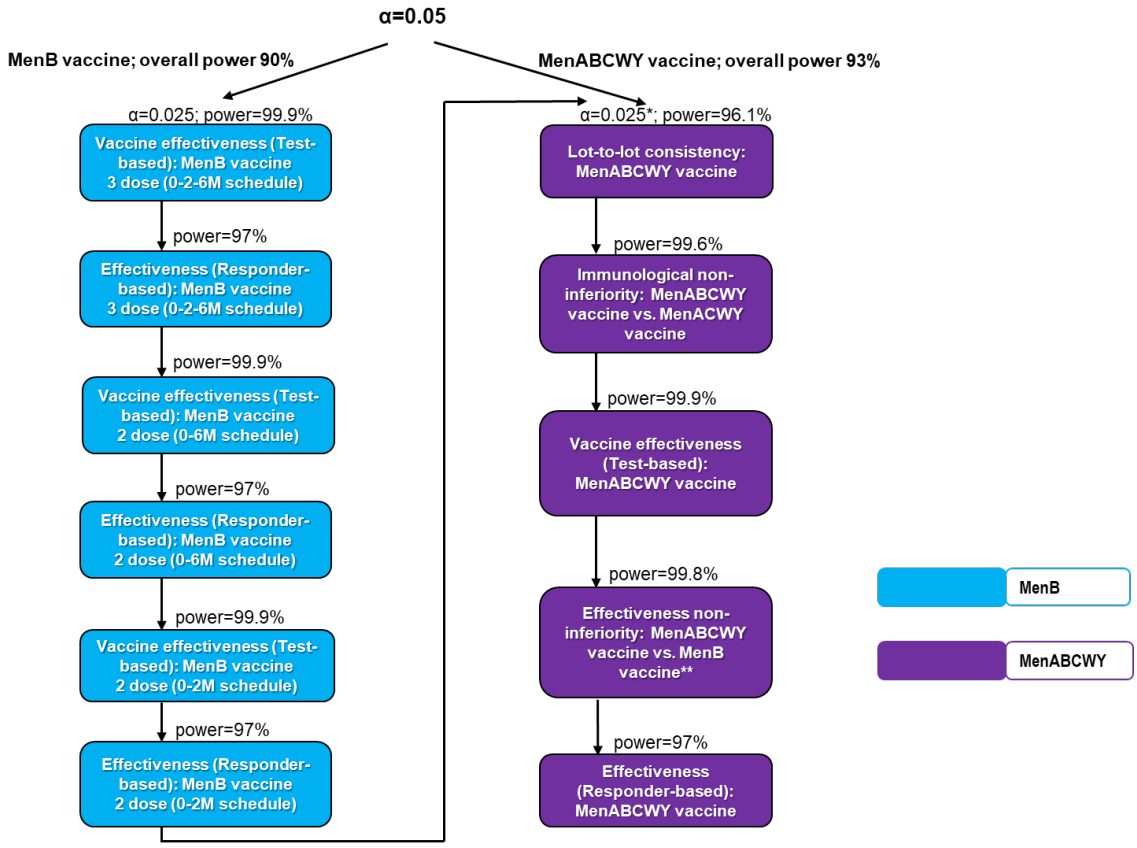
In case for a subject besides ediary data, also solicited reactions were recorded in the CRF, the CRF data will be mapped into the SDTM data with the ediary data (FA domain). For the analysis, the CRF data will be used in case of duplicate data.

6. ANALYSIS INTERPRETATION

Multiple objectives and endpoints require type I error control. Full alpha (0.05) is split equally (alpha=0.025) between rMenB+OMV NZ objectives and MenABCWY objectives. Furthermore, within rMenB+OMV NZ, as well as within MenABCWY, objectives are tested hierarchically. If the first null hypothesis is rejected, then the testing will continue with the second hypothesis at same alpha. Same for 3rd, 4th, and so forth. Whenever a null hypothesis is not rejected, then the testing will stop.

As the comparator for MenABCWY non inferiority objective for the B component will be the selected schedule of rMenB+OMV NZ as determined in this study, the objectives of rMenB+OMV NZ will be analysed first. Additionally, if all null hypotheses related to rMenB+OMV NZ objectives will be rejected, the alpha (alpha=0.025) will be propagated to the MenABCWY part, and hypotheses related to MenABCWY objectives will be tested at full alpha (alpha=0.05). See Figure 2 for an explanation of the hierarchical testing (top to bottom, the order indicated by the arrows).

Figure 2 Hierarchical testing of hypothesis



* Alpha split equally between rMenB+OMV NZ and MenABCWY vaccine objectives.
If all rMenB+OMV NZ objectives achieved, MenABCWY vaccine objectives will be tested at full alpha.
** If all objectives of rMenB+OMV NZ are met, the comparator will be the 0,2-months schedule. If the 0,2-months objective is not met, and the 0,6-months is met, then the 0,6-months schedule will be the comparator. If the 0,6-months is also not met, then the 0,2,6-months schedule will be the comparator.

Refer to Glossary of terms for definitions of test-based and responder-based vaccine effectiveness.

7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

The final study report will contain at least the final analyses of all primary and secondary endpoints.

7.2. Statistical considerations for interim analyses

No interim analysis is planned for this study

8. CHANGES FROM PLANNED ANALYSES

Not applicable

9. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

The following sections describe additional derivation rules and statistical methods which are not presented in section 10.1.

9.1. Data derivation

Not applicable

9.2. Statistical Method

Not applicable

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

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

10.1.1. Attributing events to vaccine doses

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

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

10.1.2. Handling of missing data

10.1.2.1. Dates

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

- A missing day will be replaced by 15

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

The following exceptions apply:

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

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

10.1.2.2. Laboratory data

Missing laboratory results (including immunological data) will not be replaced.

10.1.2.3. Daily recording of solicited adverse events

10.1.2.3.1. Studies with electronic diaries

For studies using electronic diaries for the collection of solicited adverse events, a solicited adverse events will be considered present only when a daily recording of grade 1 or more is present.

10.1.2.4. Unsolicited adverse events

Unsolicited adverse event summaries are including serious adverse events unless specified otherwise.

Missing severity, relationship with study vaccine, and outcome of unsolicited adverse events will not be replaced and will appear as 'UNKNOWN' in all statistical output.

10.1.3. Data derivation

10.1.3.1. Age at vaccination in days

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

Age = date of vaccination minus date of birth

10.1.3.2. Age at vaccination in months

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

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

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

10.1.3.3. Age at vaccination in years

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

DOB = 10SEP1983, Date of vaccination = 09SEP2018 -> Age = 34 years

DOB = 10SEP1983, Date of vaccination = 10SEP2018 -> Age = 35 years

10.1.3.4. Weight

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

Weight in kilograms = Weight in pounds / 2.2

10.1.3.5. Height

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

Height in centimeters = Height in inches x 2.54

10.1.3.6. Body mass index (BMI)

BMI will be calculated as follows:

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

10.1.3.7. Temperature

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

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

10.1.3.8. Numerical serology results

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

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

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

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

10.1.3.10. Onset day

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

10.1.3.11. Duration of events

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

10.1.3.12. Counting rules for combining solicited and unsolicited adverse events

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

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

10.1.3.13. Counting rules for occurrences of solicited adverse events

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

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with:

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

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

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

10.1.4.2. Differences in percentages

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

10.1.4.3. Demographic/baseline characteristics statistics

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

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

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

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

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

10.1.4.4. Serological summary statistics

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

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

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

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

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

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

10.1.5.2. Standardized asymptotic confidence intervals around differences in proportions

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

10.2. TFL TOC

The Tables Figures and Listings (TFL) Table of Contents (TOC) which itemizes the planned list of TFL and their associated lay-out is developed as a separate document.

10.3. Glossary of terms

End of Study (EoS) **(Synonym of End of Trial)**	For studies with collection of human biological samples and/or imaging data, the EoS is defined as Last subject last visit (T10). or Last testing results released of samples collected at Visit 6* * In this case EoS must be achieved no later than 8 months after LSLV.
Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.
Responder-based vaccine effectiveness:	The enc-hSBA methodology involves testing the serum samples from each individual subject against a subset of around 35 strains randomly chosen from the overall panel of 110 meningococcus B US strains. Responder-based vaccine effectiveness is assessed based on the percentage of subjects considered responders, i.e., subjects whose serum kills the majority (≥70% in this study) of the tested strains following vaccination.
Test-based vaccine effectiveness:	The enc-hSBA methodology involves testing the serum samples from each individual subject against a subset of around 35 strains randomly chosen from the overall panel of 110 meningococcus B US strains. Test-based vaccine effectiveness is assessed based on the overall percent of individual positive tests following vaccination and represents the reduction in risk compared to the placebo.

11. REFERENCES

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Statistical Analysis Plan	
Detailed Title:	A phase III, randomized, controlled, observer-blind study to demonstrate effectiveness, immunogenicity and safety of GSK's meningococcal Group B and combined ABCWY vaccines when administered to healthy adolescents and young adults.
eTrack study number and Abbreviated Title	205416 [MENB REC 2ND GEN-038 (V72_72)]
Scope:	All data pertaining to the above study
Date of Statistical Analysis Plan	Final: 12 Jan 2023

APP 9000058193 Statistical Analysis Plan Template V4 (Effective date: 3June2019)

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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
Eli Type	Internal database code for type of elimination code
ELISA	Enzyme-linked immunosorbent assay
EOS	End of Study
ES	Exposed Set
FAS	Full Analysis Set
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titre
GSK	GlaxoSmithKline
LL	Lower Limit of the confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
PCD	Primary completion Date
PPS	Per-Protocol Set
RR	Relative Risk
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
TFL	Tables Figures and Listings
TOC	Table of Contents

1. DOCUMENT HISTORY

Date	Description	Protocol Version
25 Jul 2019	First version	Amendment 1: 23 MAY 2019
15 Jun 2020	Amendment 1	Amendment 2: 18 MAR 2020
25 Mar 2022	Amendment 2	Amendment 4: 12 MAY 2021
25 Apr 2022	Amendment 3	Amendment 4: 12 MAY 2021
08 Sep 2022	Amendment 4	Amendment 4: 12 MAY 2021
12 Jan 2023	Amendment 5	Amendment 4: 12 MAY 2021

2. OBJECTIVES/ENDPOINTS

Table 1 Study objectives and endpoints

Objectives	Endpoints
Primary	
Vaccine effectiveness (Test-based): rMenB+OMV NZ To demonstrate the effectiveness of the rMenB+OMV NZ vaccine against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity using enc-hSBA at 1 month after the 3-dose (0,2,6-months) and 2-dose (0,6-months; 0,2-months) vaccination series when compared to 1 month after the MenACWY vaccination. *Criterion* *Lower limit (LL) of the two-sided 97.5% confidence interval (CI) for vaccine effectiveness is above 65% against a randomly selected strain panel between the:* • *MenB_0_2_6 and ACWY groups (for 0,2,6-months schedule)* • *MenB_0_6 and ACWY groups (for 0,6-months schedule),* • *MenB_0_2_6 and ACWY groups (for 0,2-months schedule)*	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at 1 month after the: • 3-dose vaccination series in MenB_0_2_6 group (Day 211, Month 7) • 2-dose vaccination series in MenB_0_6 group (Day 211, Month 7), and • 2-dose vaccination series in MenB_0_2_6 group (Day 91, Month 3) • 1 month after the MenACWY vaccination in ACWY group (Day 31, Month 1).
Effectiveness (Responder-based): rMenB+OMV NZ To demonstrate the effectiveness of the rMenB+OMV NZ vaccine by assessing the percentages of subjects whose sera kill ≥70% of strains tested using enc-hSBA at 1 month after the 3-dose (0,2,6-months) and 2-dose (0,6-months; 0,2-months) vaccination series of the rMenB+OMV NZ. *Criterion:* *LL of the two-sided 97.5% CI for the percentages of subjects whose sera kill ≥70% of strains is above 65%, tested for:* • *MenB_0_2_6 group (for 0,2,6-months schedule)* • *MenB_0_6 group (for 0,6-months schedule),* • *MenB_0_2_6 group (for 0,2-months schedule)*	The percentages of subjects whose sera kill ≥70% of the strains tested using enc-hSBA, at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group), • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group)
The 3 vaccine schedules will be tested for both, test-based and responder-based, in a hierarchical way (starting from 0-2-6, to 0-6 and 0-2). Refer to Protocol Section 10.1 for details on continuing the evaluation.	

Objectives	Endpoints
Lot-to-lot consistency: MenABCWY vaccine To demonstrate lot-to-lot consistency of the immune responses of 3 lots of the MenACWY component of the MenABCWY vaccine, as measured by hSBA GMTs directed against serogroups A, C, W and Y at 1 month after last vaccination (0,6-months). *Criterion:* *The two-sided 97.5% CIs^ for the ratio of hSBA GMTs of antibodies against serogroups A, C, W and Y are within the [0.5;2.0] equivalence interval for each pair of lots.*	GMTs directed against serogroups A, C, W and Y for each lot (ABCWY-1 group, ABCWY-2 group, ABCWY-3 group) at 1 month after the last vaccination (Day 211, Month 7)
Immunological non-inferiority: MenABCWY vaccine vs. MenACWY vaccine To demonstrate the immunological non-inferiority of the MenABCWY vaccine compared to the MenACWY vaccine as measured by the percentages of subjects achieving a 4-fold rise in hSBA titres against *N. meningitidis* serogroups A, C, W and Y at 1 month after the last MenABCWY vaccination (0,6-months) and 1 month after the MenACWY vaccination. *Criterion:* *LL of the 2-sided 97.5% CI^ for the group difference in percentages of subjects achieving a 4-fold rise* in hSBA titres is above -10%.*	The percentages of subjects with 4-fold rise* in hSBA titres against *N. meningitidis* serogroups A, C, W and Y at 1 month after the: • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • 1 month after the MenACWY vaccination for the ACWY group (Day 31, Month 1) relative to baseline (Day 1, Month 0).
Vaccine effectiveness (Test-based): MenABCWY vaccine To demonstrate the effectiveness of the MenABCWY vaccine against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains as measured by enc-hSBA at 1 month after the last MenABCWY vaccination (0,6-months) when compared to 1 month after the MenACWY vaccination. *Criterion:* *LL of the two-sided 97.5% CI^ for vaccine effectiveness is above 65% against a randomly selected strain panel between the ABCWY group (pooled lots) and the ACWY group.*	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at 1 month after the: • last vaccination for the ABCWY group (pooled) (Day 211, Month 7), and • 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1).
Effectiveness non-inferiority: MenABCWY vaccine vs. rMenB+OMV NZ vaccine To demonstrate the non-inferiority of the effectiveness of the MenABCWY vaccine (0,6-months schedule) compared to the rMenB+OMV NZ vaccine (0,2,6-months or 0,6-months or 0,2-months)† in terms of percentage of samples with bactericidal serum activity using enc-hSBA against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains. *Criterion:* *LL of the two-sided 97.5% CI^ for the difference in percentages of samples with bactericidal serum activity using enc-hSBA against a randomly selected panel of*	The percentages of samples with bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains at 1 month after the: • last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • 3-dose vaccination series of rMenB+OMV vaccine (Day 211, Month 7 in MenB_0_2_6 group) or 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) or 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group)†

Objectives	Endpoints
endemic US N. meningitidis serogroup B invasive disease strains is above -5% at 1 month after: • *the last vaccination in ABCWY group (pooled lots) (for 0,6 months schedule), and* • *The last vaccination in MenB_0_2_6 group (for 0,2,6-months schedule) or the last vaccination in MenB_0_6 group (for 0,6-months schedule) or the second vaccination in MenB_0_2_6 group (for 0,2-months schedule*	
Effectiveness (Responder-based): MenABCWY vaccine To demonstrate the effectiveness of MenABCWY vaccine by assessing the percentages of subjects whose sera kill ≥70% of strains tested using enc-hSBA at 1 month after the last vaccination of MenABCWY (0,6-months). *Criterion:* *LL of the two-sided 97.5% CI^ for the percentages of subjects whose sera kill ≥70% of strains tested for MenABCWY is above 65%.*	The percentages of subjects whose sera kill ≥70% of the strains tested using enc-hSBA, at 1 month after the last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7).
Safety To evaluate the safety and reactogenicity of the MenB, MenABCWY, and the MenACWY vaccines	• The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [body temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) adverse events (AEs) during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. • The frequencies and percentages of subjects with any unsolicited AEs (including all SAEs, AEs leading to withdrawal, AESIs and medically attended AEs) during the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. • The percentages of subjects with SAEs, AEs leading to withdrawal, AESIs and medically attended AEs throughout the study period [Month 0 to Month 18].
Secondary	
To demonstrate the immunological non-inferiority of the MenABCWY vaccine compared to the rMenB+OMV NZ vaccine as measured by the percentages of subjects achieving a 4-fold rise in hSBA titres against *N. meningitidis* serogroup B indicator strains at 1 month after the last MenABCWY vaccination (0,6-months schedule) and 1 month after the rMenB+OMV NZ vaccination (0,2,6-months or 0,6-months or 0,2-months)† *Criterion:* *Non-inferiority will be demonstrated if the LL of the 2-sided 95% CI for the group difference in percentage of*	The percentages of subjects with 4-fold rise** in hSBA titres against *N. meningitidis* serogroup B indicator strains at 1 month after the: • last MenABCWY vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • 3-dose vaccination series of rMenB+OMV vaccine(Day 211, Month 7 in MenB_0_2_6 group) or 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) or 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group)† relative to baseline (Day 1, Month 0).

Objectives	Endpoints
*subjects achieving a 4-fold rise** in hSBA titres against N. meningitidis serogroup B indicator strains is above -10%.*	
To assess the effectiveness of the rMenB+OMV NZ and MenABCWY vaccines against each of the randomly selected endemic US *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series when compared to 1 month after the MenACWY vaccination.	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group) • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • MenACWY vaccination (Day 31, Month 1 in ACWY group).
To describe the distribution of subjects by percentages of serogroup B invasive disease strains killed using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series of rMenB+OMV NZ and MenABCWY vaccines.	The percentages of serogroup B invasive disease strains killed using enc-hSBA in each subject at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7)
To assess the immune response to the rMenB+OMV NZ (0,2,6-months, 0,6-months and 0,2-months) and MenABCWY (0,6-months) vaccines against *N. meningitidis* serogroup B indicator strains at pre-vaccination (Day 1, Month 0) and at 1 month after the last MenABCWY vaccination and at 1 month after the second and third vaccination of rMenB+OMV NZ.	The immune response to the rMenB+OMV NZ and ABCWY vaccines will be evaluated by measuring bactericidal activity against *N. meningitidis* serogroup B indicator strains as following: *1. The percentages of subjects with hSBA titres ≥ lower limit of quantitation (LLOQ) for each (individual response) and all (composite response) serogroup B indicator strains at baseline (Day 1, Month 0) and at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *2. The percentages of subjects with 4-fold rise** in hSBA titres at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 90, Month 3 in MenB_0_2_6 group), and

Objectives	Endpoints
	• last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *relative to baseline (Day 1, Month 0).* *3. hSBA GMTs at baseline (Day 1, Month 0) and at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *4. hSBA GMRs at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *relative to the baseline (Day 1, Month 0).*
To assess the immune response to MenABCWY (0,6-months schedule) and MenACWY (single dose) vaccines against *N. meningitidis* serogroups A, C, W and Y, at pre-vaccination (Day 1, Month 0) and at 1 month after the first and the last MenABCWY vaccination and 1 month after the MenACWY vaccination.	*1. The percentage of subjects with hSBA titres ≥ LLOQ for serogroups A, C, W and Y at baseline (Day 1, Month 0) and:* • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1). *2. The percentage of subjects with 4-fold rise* in hSBA titres at 1 month after the:* • first vaccination (Day 31, Month 1) for the ABCWY group (pooled lots) compared to the MenACWY vaccination in the ACWY group (Day 31, Month 1) *relative to baseline (Day 1, Month 0).* *3. hSBA GMTs against N. meningitidis serogroups A, C, W and Y* at baseline (Day 1, Month 0) and: • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1). *4.hSBA GMRs against N. meningitidis serogroups A, C, W and Y at:* • 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots) as compared to baseline (Day 1, Month 0), and

Objectives	Endpoints
	• 1 month after the single MenACWY vaccination in the ACWY group (Day 31, Month 1) as compared to baseline (Day 1, Month 0). *5.The total IgG as measured by ELISA GMCs against serogroups A, C, W and Y* at baseline (Day 1, Month 0) and*:* • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1).

Abbreviations: ELISA = enzyme-linked immunosorbent assay; Enc-hSBA = endogenous complement human serum bactericidal assay; GMC = geometric mean concentrations; GMT = geometric mean titre; GMR = geometric mean ratio; CI = confidence interval; hSBA = human serum bactericidal assay; LOD: limit of detection; LLOQ = lower limit of quantitation; LL = lower limit; AE = Adverse event; SAE = Serious adverse event; AESI = Adverse event of special interest

N.meningitidis serogroup B indicator strains = M14459, 96217, M07-0241084 and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively. The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented either in a protocol amendment or in the clinical report.

Refer to Protocol Section 10 for details on evaluation of objectives and sample size justification. Refer to Glossary of terms for definitions of test-based and responder-based effectiveness

^ If the co-primary effectiveness objectives for rMenB+OMV NZ are met, then all objectives for MenABCWY will be evaluated at 95% CI. Refer to Protocol Section 10.1 for details

P† PIf all objectives of rMenB+OMV NZ are met, the comparator will be the 0,2-months schedule. If the 0,2-months objective is not met, and the 0,6-months is met, then the 0,6-months schedule will be the comparator. If the 0,6-months is also not met, then the 0,2,6-months schedule will be the comparator.

*For the Men A, C, W, Y evaluation, the 4-fold rise is defined as:

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

**For the MenB evaluation, the 4-fold rise per each indicator strain is defined as:

- a post-vaccination‡ hSBA titre ≥4 times the LOD for subjects with a pre-vaccination hSBA titre <LOD
- a post-vaccination‡ hSBA titre ≥4 times the LLOQ for subjects with a pre-vaccination hSBA titre ≥LOD and <LLOQ, and
- a post-vaccination‡ hSBA titre ≥4 times the pre-vaccination hSBA titre for subjects with a pre-vaccination hsBA titre ≥LLOQ

‡ = post-2nd vaccination for 0,6 and 0,2 schedule and post-3rd vaccination for 0,2,6 schedule.

3. STUDY DESIGN

3.1. Scientific rationale for study design

As the rMenB+OMV NZ licensure in the US was issued through accelerated approval, the FDA has requested to demonstrate the effectiveness of the vaccine against an extended panel of serogroup B meningococcal strains (MenB) as a post-marketing commitment in US adolescents and young adults, thus confirming that the vaccine can protect against diverse meningococcal B strains prevalent in the United States.

The availability of a pentavalent meningococcal vaccine in a single administration would however reduce the number of injections and could increase coverage for meningococcal disease caused by *N. meningitidis* serogroups A, B, C, W, and Y worldwide. GSK's investigational MenABCWY combination vaccine is intended to protect against 5 of the most prevalent serogroups of *Neisseria meningitidis* (A, B, C, W, Y) in humans.

Hence, along with the licensed MenB vaccine (*Bexsero*), this Phase III study will also assess the safety, effectiveness, and immunogenicity of the investigational MenABCWY vaccine.

Rationale for effectiveness assessment

As mentioned above, one of the primary purposes of this study is to evaluate the effectiveness of 2 or 3 doses of rMenB+OMV NZ and of 2 doses of the MenABCWY vaccines in healthy adolescents and young adults by measuring the bactericidal activity against 110 endemic US *N. meningitidis* serogroup B strains using an endogenous complement human Serum Bactericidal Assay (enc-hSBA). Sera from the ACWY group receiving the MenACWY vaccine will also be tested against serogroup B meningococcal strains by enc-hSBA as a control for test-based effectiveness assessment. The overall vaccine effectiveness (VE) against all 110 strains combined will be computed by means of a generalised linear model. For additional details see statistical analysis section of the Clinical Study Protocol (Protocol Section 10).

Rationale for lot-to-lot consistency assessment

MenABCWY is a reconstituted vaccine with the lyophilised 'ACWY component' and liquid rMenB+OMV NZ. The MenB component has the same formulation as the commercial *Bexsero*. To demonstrate that the lots of the investigational MenABCWY vaccine are adequately representative of the formulation intended for marketing, equivalence will be assessed for 3 different lots of the ACWY component of the ABCWY vaccine.

Rationale for non-inferiority assessment of MenABCWY vs MenACWY and rMenB+OMV NZ

The study aims to also demonstrate that the investigational combination MenABCWY vaccine is not inferior to a licensed MenACWY vaccine (*Menveo*) and a licensed MenB vaccine (*Bexsero*) which are part of the current standards of care in the US for prevention of invasive disease caused by *N. meningitidis* serogroups A, C, W, Y and by *N. meningitidis* serogroup B, respectively.

Rationale for blood volume collected:

In order to provide the necessary serum volume for the bactericidal assays (enc-hSBA and/ or hSBA(s)), 25 mL whole blood will be collected at Visit 2, Visit 4 and Visit 6. At pre-vaccination (Visit 1), 20 mL whole blood will be collected to provide the necessary serum volume for the hSBA.

Blood samples are taken from all subjects irrespective of the testing status in order to maintain the study blind. Refer to Protocol Section 8.4.2.1 for further details.

Rationale for the selected vaccination schedules

rMenB+OMV NZ: This study aims at demonstrating the VE of the rMenB+OMV NZ vaccine administered as 2-dose vaccine, either with a shorter interval (0,2-months) or a prolonged interval (0,6-months) between doses. A 3-dose schedule has been also added to better characterise the VE.

Note: The rMenB+OMV NZ in the ACWY group is administered in a 0,1-months schedule. This interval is within the recommendations in the summary of product characteristics of *Bexsero* and helps in maintaining the blind. No objectives are associated with this schedule of rMenB+OMV NZ.

MenABCWY: A number of different vaccine formulations were evaluated in MenABCWY Phase I and II clinical studies. The formulation with the same active ingredient composition as the rMenB+OMV NZ (*Bexsero*) and MenACWY (*Menveo*) vaccines was chosen as the final formulation of the investigational MenABCWY vaccine. Two doses administered 6 months apart (0,6-months) is considered the optimal dosing schedule, based on serogroup B immunogenicity results from MenABCWY Phase II clinical studies.

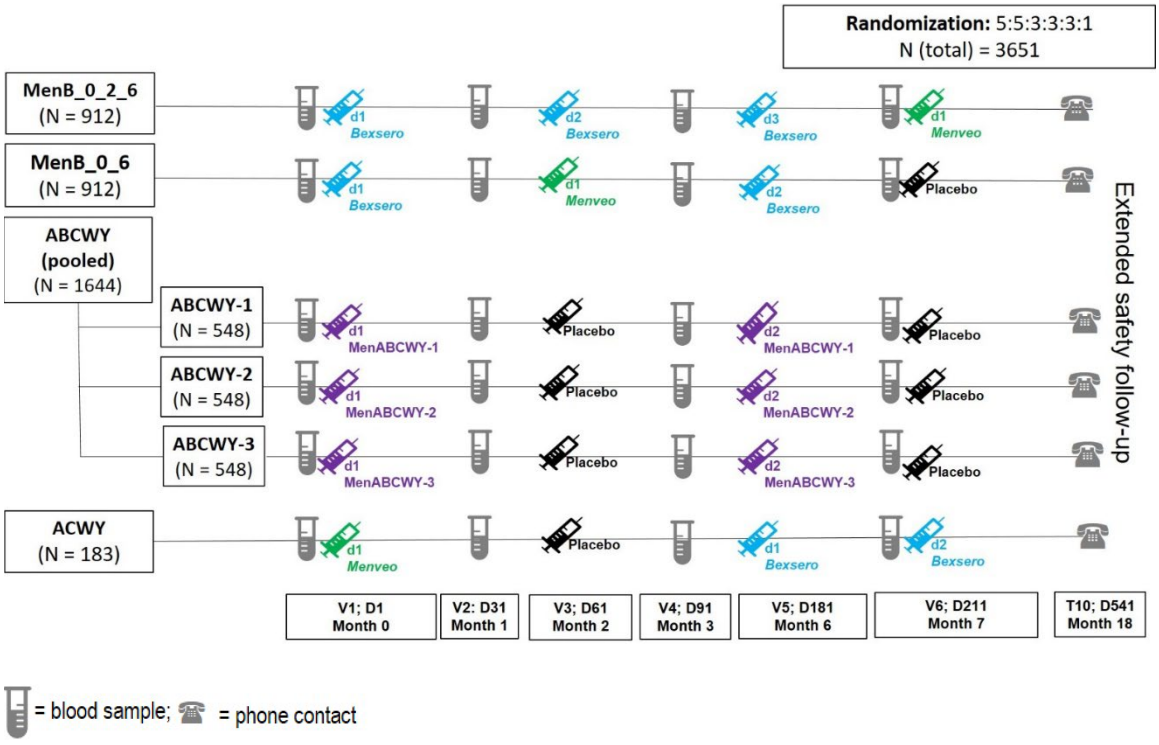
MenACWY: As a comparator for serogroup A, C, W, and Y vaccine effectiveness and immune responses, a single dose of MenACWY vaccine is administered to subjects in the ACWY group. To conform with the standard of care (also in alignment with current ACIP routine immunisation recommendations in US), subjects in the MenB_0_2_6 and MenB_0_6 groups will also receive a dose of MenACWY at Day 211 and Day 61, respectively.

3.1.1. Rationale for the use of placebo

For this study, a placebo (saline solution) will be administered as presented in Figure 1. A placebo is the only available option to minimize possible introduction of reporting bias in collecting information about AEs and to ensure the same number of vaccinations are administered to subjects assigned to either of the six study groups.

3.2. Overall design

Figure 1 Study design overview



N = number of subjects; d = dose; V = visit; D = day; T=Telephone call
Refer to Protocol Table 3 for details on all visits
Note: Home visits may be performed only by sites authorised (as per local regulations and sponsor agreement), with approved site level standard operating procedures (SOP) provided that the compliance with protocol procedures are ensured.

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the schedule of activities (Protocol Section 2), are essential and required for study conduct.

- Type of study: self-contained

- Experimental design: This is a phase III, randomised, controlled, observer-blind, multi-center study to evaluate effectiveness, immunogenicity and safety of rMenB+OMV NZ and MenABCWY vaccines. A total of 3651 healthy adolescents and young adults aged 10-25 years will be enrolled and randomised (5:5:3:3:3:1 ratio) to one of the six parallel study groups:

  – **MenB_0_2_6 group***: subjects will receive 3 doses of rMenB+OMV NZ at Day 1, Day 61 and Day 181 (0, 2 and 0,2,6-months schedule). These subjects will receive 1 dose of the MenACWY vaccine at Day 211**.

  – **MenB_0_6 group**: subjects will receive 2 doses of rMenB+OMV NZ at Day 1 and Day 181 and 1 dose of MenACWY vaccine at Day 61 (rMenB+OMV NZ, 0,6-months schedule). These subjects will receive 1 dose of placebo at Day 211**.

  – **ABCWY-1**: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 1 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211**.

  – **ABCWY-2**: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 2 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211**.

  – **ABCWY-3**: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 3 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211**.

  – **ACWY group**: subjects will receive 1 dose of MenACWY vaccine at Day 1, 1 dose of placebo at Day 61 and 2 doses of rMenB+OMV NZ at Day 181 and Day 211**.

  * MenB_0_2_6 group will also be evaluated for objectives pertaining to 0,2-months vaccination schedule.

  Note 1: A MenB lot will be used for the pre-filled syringe component of the MenABCWY vaccine.

  Note 2: The groups ABCWY-1, ABCWY-2, ABCWY-3 will be pooled into a single group, ABCWY (pooled lots) (except for analysis of lot to lot consistency).

  ** Note 3: In order to let the subjects in MenB_0_2_6 group receive a dose of MenACWY vaccine and for subjects in ACWY group to receive the second dose of rMenB+OMV NZ in line with the vaccine as standard of care (also in line with the Advisory Committee on Immunization Practices (ACIP) recommendations in the US [ACIP, 2011]), the subjects in these groups will receive a vaccination of MenACWY and rMenB+OMV NZ vaccines, respectively, on Day 211 (Visit 6) after completion of the post-vaccination 3 blood sampling. To maintain the blinding of the study, subjects in the rest of the groups (MenB_0_6, ABCWY-1, ABCWY-2 and ABCWY-3) will receive a dose of Placebo. All these vaccines/ product administered at Day 211 are not associated with any study objectives/ endpoints (Safety assessment

conducted after 1 dose of rMenB+OMV NZ in the ACWY group at Day 181 is to maintain the blind of the study).

- Duration of the study: The study duration is approximately 18 months for each subject.
- Primary completion Date (PCD): T10; Day 541.

Refer to Glossary of terms for the definition of PCD.

- End of Study (EoS): the date of release of the last testing results, to be achieved not later than 8 months after Last Subject Last Visit (LSLV) (LSLV = T10; Day 541). If the completion of testing occurs prior the completion of the LSLV the latter date defines the end of study visit.

Refer to Glossary of terms for the definition of EoS.

- Study groups:

Table 2 Study groups and treatment foreseen in the study

Study Groups	Number of subjects	Age (Min-Max)	Treatment name	Vaccine/Product name
MenB_0_2_6	912	10 – 25 y	*Bexsero* (Injection)	rMenB+OMV NZ
			Menveo (Injection)	MenACWY
MenB_0_6	912		*Bexsero* (Injection)	rMenB+OMV NZ
			Menveo (Injection)	MenACWY
			Placebo (Injection)	NaCl
ABCWY-1	548		MenABCWY (with Lot 1 of ACWY) (Injection)	MenABCWY-1
			Placebo (Injection)	NaCl
ABCWY-2	548		MenABCWY (with Lot 2 of ACWY) (Injection)	MenABCWY-2
			Placebo (Injection)	NaCl
ABCWY-3	548		MenABCWY (with Lot 3 of ACWY) (Injection)	MenABCWY-3
			Placebo (Injection)	NaCl
ACWY	183		*Menveo* (Injection)	MenACWY
			Placebo (Injection)	NaCl
			Bexsero (Injection)	rMenB+OMV NZ

Table 3 Overview of study design: Vaccination and Blood Draw Schedule

Visits **Study Day**	**Visit 1** **Day 1**	Visit 2 Day 31	**Visit** 3 **Day 61**	**Visit** 4 **Day 91**	**Visit** 5 **Day 181**	**Visit** 6 **Day 211**
Group **MenB_0_2_6** **N=912**	Pre-vacc Blood sample rMenB+OMV NZ	Post-vacc 1 Blood sample	rMenB+OMV NZ	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample MenACWY
Group **MenB_0_6** **N=912**	Pre-vacc Blood sample rMenB+OMV NZ	Post-vacc 1 Blood sample	MenACWY	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample Placebo
Group **ABCWY-1** **N=548**	Pre-vacc Blood sample MenABCWY-1	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-1	Post-vacc 3 Blood sample Placebo
Group **ABCWY-2** **N=548**	Pre-vacc Blood sample MenABCWY-2	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-2	Post-vacc 3 Blood sample Placebo
Group **ABCWY-3** **N=548**	Pre-vacc Blood sample MenABCWY-3	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-3	Post-vacc 3 Blood sample Placebo
Group **ACWY** **N=150**	Pre-vacc Blood sample MenACWY	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample rMenB+OMV NZ

N = number of subjects; Pre-vacc = pre-vaccination; Post-vacc = post-vaccination

- Treatment allocation: At Day 1, prior to the study vaccination, subjects will be randomised to 1 of the 6 study groups according to a 5:5:3:3:3:1 ratio.
- Blinding: Observer-blind. Kindly refer to Protocol Section 7.3 for details on blinding and unblinding procedures.
- Sampling schedule:
  - A total of 4 blood samples* will be collected from each subject at Day 1 (pre-vaccination blood sample; approximately 20 mL), at Day 31 (post-vaccination 1 blood sample; approximately 25 mL), at Day 91 (post-vaccination 2 blood sample; approximately 25 mL) and at Day 211 (post-vaccination-3 blood sample; approximately 25 mL).
  - Urine sampling: Urine samples for pregnancy testing will be collected from female subjects of child-bearing potential at Visit 1 (Day 1), Visit 3 (Day 61), Visit 5 (Day 181) and Visit 6 (Day 211) prior to the vaccination.

  * Insufficient blood volume may lead to test cancellation and jeopardise the statistical power. Hence, every effort must be done to collect blood volume as per protocol requirements.
- Data collection: standardised Electronic Case Report Form (eCRF). Solicited symptoms will be collected using a subject Diary (electronic Diary [eDiary]).
- Safety monitoring: Regular safety follow-up will be done through telephone calls (T). There will also be an extended safety follow-up (ESFU) phone call 12 months post-vaccination 3 (Day 181; Visit 5). This ESFU phone call will also mark the study conclusion. Refer to Protocol Table 3 and Protocol Section 8.5.3 for details on the safety follow-up.

3.3. Number of subjects

A total of 3651 subjects will be randomised in a ratio of 5:5:3:3:3:1; 912 each in MenB_0_2_6 and MenB_0_6 groups, 548 in each ABCWY groups and 183 in ACWY group. Assuming a 25% drop out rate, this should provide approximately 684 evaluable subjects in each of the MenB groups, 411 evaluable subjects in each of the ABCWY groups and 137 evaluable subjects in the ACWY group.

Refer to Protocol Section 10.1 for a detailed description of the criteria used in the determination of sample size.

Withdrawals will not be replaced.

3.4. Subject and study completion

A subject is considered to have completed the study, if the subject is available for the concluding contact (T10; Day 541) as described in the protocol.

Global completion of the study is required in order to provide enough subjects as defined in Protocol Section 10.1 Sample Size Determination.

4. ANALYSIS SETS

4.1. Definition

For purposes of analysis, the following analysis sets are defined:

4.1.1. Enrolled Set

Subject/ Subject for whom parent(s)/LAR's agreed to participate in a clinical study after completion of the informed consent process, who meet screening/eligibility criteria and randomized and/or received study intervention or undergone an invasive procedure.

4.1.2. Exposed Set

All subjects who received at least 1 dose of the study treatment. The allocation in a group is done in function of all administered treatments.

4.1.3. Full Analysis Set

All subjects who received at least 1 dose of the study treatment and have post-vaccination effectiveness or immunogenicity data.

4.1.4. Per Protocol Set

All subjects in the Full Analysis Set minus subjects with protocol deviations that lead to exclusion from the Per Protocol Set.

4.1.5. Solicited Safety Set

All subjects who received at least 1 dose of the study treatment (Exposed Set) who have solicited safety data beyond 30 minutes post vaccination.

4.1.6. Unsolicited Safety Set

All subjects who received at least 1 dose of the study treatment (Exposed Set) that report unsolicited AEs/report not having unsolicited AEs.

4.1.7. Overall Safety Set

All subjects that belong to the Unsolicited safety or/and to the Solicited safety set.

4.2. Criteria for eliminating data from Analysis Sets

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

4.2.1. Elimination from Exposed Set (ES)

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

4.2.2. Elimination from Per protocol Set (PPS)

4.2.2.1. Excluded subjects

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

Table 4 Elimination code and condition to exclude a subject from the PPS analysis

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
800	Fraudulent data	All	All
900	Invalid informed consent	All	All
1030	Study vaccine not administered at all	All	All
1050	Randomization failure	Visit 1, 3, 5	All
1060	Randomization code was broken	All	All
1070.1	Subjects got vaccinated with the correct vaccine but containing a lower volume	Visit 1, 3, 5	All
1070.2	Vaccination not according to protocol	Visit 1, 3, 5	All
1080	Vaccine temperature deviation	Visit 1, 3, 5	All
1090	Expired vaccine administered	Visit 1, 3, 5	All
1500.1	Other deviation from study procedures not able to classified under any other categories	All	All
1500.2	Any other GCP non-compliance not able to classified under any other categories	All	All
2010	Protocol violation (inclusion/exclusion criteria)	All	All
2040	Administration of any medication forbidden by the protocol	Visit 1, 3, 5	All
2050	Not withdrawn after developing withdrawal criteria other than prohibited concomitant vaccination/medication (medical condition forbidden)	All	All
2060	Concomitant infection related to the vaccine which may influence immune response (only meningococcal infection)	All	All
2080	Subjects did not comply with vaccination schedule	Visit 3, 5	All

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
2090	Subjects did not comply with blood sample schedule	Visit 2, 4, 6	All
2100	Serological results not available post-vaccination for all tests	Visit 2, 4, 6	All
2120	Obvious incoherence or abnormality or error in data related to testing	Visit 2, 4, 6	All
2130	Biological sample specimen procedures not compliant with protocol	Visit 2, 4, 6	All

4.2.3. Elimination from unsolicited and solicited safety set

4.2.3.1. Excluded subjects

4.2.3.1.1. Unsolicited safety set

Code 1030 (Study vaccine not administered at all), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1150 (no post-vaccination safety data) will be used for identifying subjects eliminated from the unsolicited safety set.

4.2.3.1.2. Solicited safety set

Code 1030 (Study vaccine not administered at all), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1160 (no post-vaccination solicited safety data) will be used for identifying subjects eliminated from the solicited safety set.

5. STATISTICAL ANALYSES

Standard data derivation rules and statistical methods are described in section 10.1 while the study specific data derivation rules and stat methods are described in section 9.

5.1. Disposition of subjects

5.1.1. Analysis of disposition of subjects planned in the protocol

Number of subjects enrolled, vaccinated subjects (at least 1 vaccination, full vaccination course), reason for early withdrawal, FAS, and PPS will be described by vaccine group.

5.1.2. Additional considerations

Not applicable

5.2. Demography and baseline characteristics analyses

5.2.1. Analysis of demography and baseline characteristics planned in the protocol

Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age, height, weight, and body mass index (BMI) at enrolment will be calculated overall and by vaccine group.

Distributions of subjects by sex, race, ethnic origin will be summarised overall and by vaccine group.

5.2.2. Additional considerations

A summary table of important protocol deviations related to COVID-19 will be provided. Also, a listing will be produced.

5.3. Primary effectiveness and immunogenicity

5.3.1. Analysis of primary effectiveness and immunogenicity planned in the protocol

Refer to Glossary of terms for definitions of test-based and responder-based vaccine effectiveness. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then all objectives for MenABCWY will be evaluated at 95% CI (Sections 5.3.1.7 through 5.3.1.11, ref Protocol Section 10.1).

5.3.1.1. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Analysis set: Per-protocol set (PPS) will be the primary analysis population

Statistical method: The VE is defined as 1- RR= (1- percentage of samples without bactericidal serum activity at 1:4 dilution in MenB group / percentage of samples without bactericidal serum activity at 1:4 dilution in the ACWY group) x100% and it will be analyzed using a generalised linear model with vaccine group, strain, and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) as independent variables. Furthermore, a repeated statement will be used to estimate the variance of the RR including correlation within subject's responses to different strains. If the statistical model does not converge due to (one of) the factor(s), a model without this/these factor(s) will be fitted instead. The response variable of the model will be the Bernoulli distributed outcome without bactericidal activity at a 1:4 dilution (i.e. response is 1 if titre < 4, and 0 if titre ≥ 4), at 1 month after the last vaccination (Month 7) in the MenB group and at Month 1 for the ACWY group. Each subject will contribute with approximately 35 measures to this analysis, each of the measures corresponding to the response variable to one of the 35 strains randomly assigned to be tested with the samples available for that specific subject.

In order to obtain the VE measure which is a measure based on the relative risk (RR), a generalised linear model will be used with the Binary distribution and link function log in order to compute the log RR and the corresponding 97.5% CI. The obtained values will be exponentiated to obtain the RR and the corresponding 97.5% CI. The VE will be computed as 100% x (1 – RR). Effectiveness of rMenB+OMV NZ (0,2,6-months schedule) will be demonstrated if the lower limit of the two-sided 97.5% CI for VE between MenB and the ACWY group is above 65%.

5.3.1.2. Effectiveness (Responder-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Analysis set: FAS will be the primary analysis population.

Statistical method: The percentage of responders (see definition in Glossary of terms) and the corresponding exact two-sided 97.5% CI based on Clopper-Pearson method will be calculated [Clopper, 1934].

The objective is to demonstrate that the lower limit of the 97.5% CI for the percentage of responders is higher than 65%.

5.3.1.3. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 5.3.1.1

5.3.1.4. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 5.3.1.2

5.3.1.5. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 5.3.1.1

5.3.1.6. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 5.3.1.2

5.3.1.7. Lot-to-lot consistency: MenABCWY - ACWY component

Analysis set: The analysis of lot-to-lot consistency will be based on the PPS.

Statistical method: For each of the three ABCWY lots (Lots 1, 2 and 3 of the MenACWY component of the ABCWY vaccine), GMTs and 97.5% CIs will be calculated by exponentiating (base 10) the least squares means and the lower and upper limits of the 97.5% CIs of the log transformed titres (base10) obtained from an Analysis of Variance

(ANOVA) with factors for vaccine lot and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)). Additionally, lot-to-lot GMT ratios will be computed for each pair of ABCWY lots. Ninety-seven point five percent (97.5%) CIs for the ratios of GMTs will be constructed by exponentiating the difference of the least square means of the log transformed titres and the lower and upper limits of the 97.5% CIs on the difference obtained from the ANOVA model above.

Lot-to-lot consistency criterion: The three ABCWY lots will be considered equivalent if for each of the 4 serogroups A, C, W and Y and each pair of vaccine lots, the two-sided 97.5% CI on the ratio of GMTs at 1 month after the last vaccination will be contained within the interval [0.5, 2.0].

If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.1.8. Immunological non-inferiority: MenABCWY vs. MenACWY

Analysis set: PPS restricted to subjects without previous ACWY vaccination will be the primary analysis population.

Statistical method: The percentage of subjects with 4-fold riseP*P in hSBA titres against MenACWY indicator strains A, C, W and Y and the corresponding exact two-sided 97.5% CIs based on Clopper-Pearson method will be calculated for the ABCWY (pooled lots) group and the ACWY group [Clopper, 1934]. The 97.5% CIs for the difference in percentages between ABCWY (pooled lots) and ACWY group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-Inferiority criterion: Non-inferiority of MenABCWY vaccine for the proportion of subjects with 4-fold rise will be demonstrated if the lower limit of the two-sided 97.5% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY (pooled) lots –ACWY) is above -10%.

* For the Men A, C, W, Y evaluation, the 4-fold rise is defined as:

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

Table 5 reads the LOD and LLOQ of MenACWY indicator strains used in the definition of 4-fold rise provided by the laboratory.

Table 5 LOD and LLOQ of MenACWY indicator strains

Strain	LOD	LLOQ
Men A (3125)	CCI [redacted]	
Men C (C11)		
Men W (240070)		
Men Y (860800)		

If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.1.9. Vaccine effectiveness (Test-based): MenABCWY

See Section 5.3.1.1. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the VE for MenABCWY will be evaluated at 95% CI.

5.3.1.10. Effectiveness non-inferiority: MenABCWY vs. rMenB+OMV NZ

Analysis set: PPS will be the primary analysis population.

Statistical method: The percentage of samples with bactericidal activity measured by enc-hSBA at 1:4 dilution and the corresponding exact two-sided 97.5% CIs based on Clopper-Pearson method will be calculated for the ABCWY (pooled lots) group and the MenB group comparator that will be selected (ref: the footnote of Figure 2). The 97.5% CIs for the difference in percentages between ABCWY (pooled lots) and selected MenB group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-Inferiority criterion: Non-inferiority of MenABCWY vaccine for the percentage of samples with bactericidal activity measured by enc-hSBA at 1:4 dilution will be demonstrated if the lower limit of the two-sided 97.5% CI for the difference between the 2 groups (ABCWY (pooled) lots – MenB) is above -5%.

If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.1.11. Effectiveness (Responder-based): MenABCWY

See Section 5.3.1.2. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the effectiveness (responder-based) for MenABCWY will be evaluated at 95% CI.

5.3.2. Additional considerations

Analyses of the primary effectiveness and immunogenicity objectives will be repeated by age group (10-17 years of age and 18-25 years of age), race, sex, region (US/ ex-US), and subjects with and without a previous MenACWY vaccination (primed and unprimed).

5.3.2.1. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

The SAS code to analyse the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) objective is specified below. Treatment, region, age category, previous ACWY vaccination, and strains will be modelled as fixed effect. To account for a possible over-dispersion, the DSCALE option in the model statement will be evaluated first. The DSCALE will be kept in the model only if the F-statistics for the DSCALE parameter is significant ($p<0.05$). The following SAS code will be used for the VE calculation:

```
ods trace on;
ods output GEEEmpPEst = genmod_stats
CONVERGENCESTATUS = converge ;

PROC GENMOD data=dataset descending;
class trtgrp strain region agecat previousACWY subject_id ;
model outcome = trtgrp strain region agecat previousACWY / dist= bin
link= log DSCALE;
repeated subject = subject_id / type= CS withinsubject= strain;
estimate 'MenB026-ACWY' trtgrp 1 0 0 0 0 -1/ alpha=0.025 exp;

/*trtgrp R is MenB0,2,6 and trtgrp W is ACWY*/

run;

ods output close;

data genmod_stats;
set genmod_stats;
where parm = 'trtgrp' and level1 = '1';
rr = exp(estimate);
ub = exp(uppercl);
ve = (1 - rr)*100 ;
ve_ll = (1 - ub) * 100 ;
if ve_ll > 65 then success = 1 ;
else success = 0 ;
run;
```

where outcome represents the Bernoulli distributed outcome without bactericidal activity at a 1:4 dilution (i.e. response is 1 if titre < 4, and 0 if titre ≥ 4), one month after the 3rd vaccination in MenB 0,2,6 and one month after the MenACWY vaccination for the ACWY arm, trtgrp indicates the vaccine groups, strain is the serogroup B strain variable, region is either US or ex-US, agecat is the age at enrolment (10-17 YoA or 18-25 YoA), and previousACWY is previous ACWY vaccination (y/n) at enrolment.

rr is the relative risk (RR), which is obtained from the estimated parameters from PROC GENMOD. Vaccine effectiveness (VE) is then derived as (1-rr)x100%.

ub represents the upper bound of the 97.5% CI of the relative risk. ve_ll is the lower bound of the 97.5% CI for VE, if the value is greater than 65%, then the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) objective is successful.

5.3.2.2. Effectiveness (Responder-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Not applicable

5.3.2.3. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 5.3.2.1, with the difference in the treatment arm:

```
PROC GENMOD data=dataset descending;
class trtgrp strain region agecat previousACWY subject_id ;
model outcome = trtgrp strain region agecat previousACWY / dist= bin
link= log DSCALE ;
repeated subject = subject_id / type= CS withinsubject= strain ;
estimate 'MenB06-ACWY' trtgrp 0 1 0 0 0 -1/ alpha=0.025 exp;

/*trtgrp S is MenB0,6 and trtgrp W is ACWY*/

run;
```

5.3.2.4. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

Not applicable

5.3.2.5. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 5.3.2.1, with the difference the outcome data for group R is from one month after the 2nd vaccination instead of one month after the 3rd vaccination.

5.3.2.6. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

Not applicable

5.3.2.7. Lot-to-lot consistency: MenABCWY - ACWY component

Not applicable

5.3.2.8. Immunological non-inferiority: MenABCWY vs. MenACWY

As a sensitivity analysis, a parametric model will be run. A generalized linear model with factors for vaccine group and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA)) will be ran, with the Binary distribution and link function is identity, and outcome is 4-fold rise. If the lower limit of the two-sided 97.5% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY (pooled) lots –ACWY) coming from the model is above -10%, also the sensitivity analysis has demonstrated non-inferiority. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.2.9. Vaccine effectiveness (Test-based): MenABCWY

See Section 5.3.2.1, with the difference in the estimate statement:

```
PROC GENMOD data=dataset descending;
class trtgrp strain region agecat previousACWY subject_id ;
model outcome = trtgrp strain region agecat previousACWY / dist= bin
link= log DSCALE ;
repeated subject = subject_id / type= CS withinsubject= strain ;
estimate ' MenABCWY-ACWY' trtgrp 0 0 1 1 1 -3/ alpha=0.025 exp
divisor=3;

/*trtgrp T, U, and V are the ABCWY-1, ABCWY-2, and ABCWY-3 lots and
trtgrp W is ACWY*/
run;
```

5.3.2.10. Effectiveness non-inferiority: MenABCWY vs. rMenB+OMV NZ

As a sensitivity analysis, a parametric model will be run. A generalized linear model with factors for vaccine group and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) will be ran, with the Binary distribution and link function is identity, and outcome is bactericidal activity measured by enc-hSBA at 1:4 dilution. If the lower limit of the two-sided 97.5% CI for the difference in percentage of samples with bactericidal activity measured by enc-hSBA at 1:4 dilution between the 2 groups (ABCWY (pooled) lots –MenB) coming from the model is above -5%, also the sensitivity analysis has demonstrated non-inferiority. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

In addition to the comparison of MenABCWY vs the selected MenB schedule per Section 5.3.1.10, MenABCWY will be compared to the other MenB schedule/schedules, whichever is applicable in the same way as described in Section 5.3.1.10. If MenB 0,2 schedule is selected as comparator, in addition MenABCWY will be compared to Menb 0,6 and MenB 0,2,6 schedule. If MenB 0,6 schedule is selected as comparator, in addition MenABCWY will be compared to MenB 0,2,6 schedule. No success criterion is defined for these group comparisons.

5.3.2.11. Effectiveness (Responder-based): MenABCWY

Not applicable

5.4. Secondary effectiveness and immunogenicity

5.4.1. Analysis of secondary effectiveness and immunogenicity planned in the protocol

5.4.1.1. Immunological non-inferiority: MenABCWY vs. rMenB+OMV NZ

Analysis set: PPS will be the primary analysis population.

Statistical method: The percentages of subjects with 4-fold rise** in hSBA titres against N. meningitidis serogroup B indicator strains (M14459, 96217, M07-0241084* and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively) at 1 month after the last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) and 1 month after the 3-dose vaccination series (Day 211, Month 7) in MenB_0_2_6 group or 2-dose vaccination series (Day 211, Month 7) in MenB_0_6 group or 2-dose vaccination series (Day 91, Month 3) in MenB_0_2_6 group and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated [Clopper, 1934]. The 95% CIs for the difference in percentages between ABCWY group (pooled lots) and MenB_0_2_6 group and MenB_0_6 group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-inferiority criterion: Non-inferiority of MenABCWY vaccine for the proportion of subjects with 4-fold rise will be demonstrated if the lower limit of the 2-sided 95% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY group (pooled lots) –selected MenB group) is above -10%.

* The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented either in a protocol amendment or in the clinical report.

** For the MenB evaluation, the 4-fold rise per each indicator strain is defined as:

- a post-vaccination‡ hSBA titre ≥4 times the LOD for subjects with a pre-vaccination hSBA titre <LOD
- a post-vaccination‡ hSBA titre ≥4 times the LLOQ for subjects with a pre-vaccination hSBA titre ≥LOD and <LLOQ, and
- a post-vaccination‡ hSBA titre ≥4 times the pre-vaccination hSBA titre for subjects with a pre-vaccination hSBA titre ≥LLOQ

‡ = post-2nd vaccination for 0,6 and 0,2 schedule and post-3rd vaccination for 0,2,6 schedule).

Table 6 reads the LOD and LLOQ of hSBA titres against N. meningitidis serogroup B indicator strains used in the definition of 4-fold rise provided by the laboratory.

Table 6 LOD and LLOQ of hSBA titres against N. meningitidis serogroup B indicator strains

Strain	LOD	LLOQ
NZ98-254	CCI [redacted]	
96217		
M14459		
M13520		

5.4.1.2. Effectiveness by each of the endemic US N. meningitidis serogroup B strains

Analysis set: FAS will be the primary analysis population. The ABCWY (pooled lots) group and the MenB group comparator that will be selected (ref: the footnote of Figure 2) will be used for the purpose of this analysis.

Statistical method: The VE per strain will be calculated as described in Section 5.3.1.1, using a generalised linear model with vaccine group, and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) as independent variables, and alpha=0.05 leading to 95% CI. In case for a strain 100% response will be observed in both vaccine groups, VE against these strain will be assessed by calculating 95% CI for relative risk from raw proportions, and VE=1-RR.

5.4.1.3. Distribution of percentages of serogroup B invasive disease strains killed

Analysis set: FAS will be the primary analysis population. The ABCWY (pooled lots) group and the MenB group comparator that will be selected (ref: the footnote of Figure 2) will be used for the purpose of this analysis.

Statistical method: Summary statistics of the percentage of serogroup B invasive disease strains killed within a subject using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series of rMenB+OMV NZ and MenABCWY vaccines.

Summary statistics and 95% CI for the mean percentage will be presented, as well as a Figure of the cumulative distribution function.

5.4.1.4. Immune response of MenABCWY, rMenB+OMV NZ and MenACWY

Analysis set: The analysis will be based on the FAS.

Statistical method: The hSBA titres at each time point for all groups (ABCWY group (pooled lots), MenB_0_2_6 and MenB_0_6 groups) will be logarithmically transformed (base10) to fulfil the normal distribution assumption. For each N. meningitidis serogroup A, C, W and Y and each B indicator strain (M14459, 96217, M07-0241084* and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively), the GMTs and GMRs (post-vaccination/baseline) will be obtained from an Analysis of Variance (ANOVA) with factors for vaccine group, region (US/ex-US), age category (10-17 YoA/18-25 YoA), and previous MenACWY vaccination (y/n), and then exponentiating the log-transformed means and their 95% CIs. The ratio of GMTs and GMRs between two groups and the corresponding CI will be estimated additionally.

The total IgG (as measured by ECL) against serogroups A, C, W and Y at baseline (Day 1, Month 0) and

- at 1 month after the first (Day 31, Month 1) and the last vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and
- at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1),

will be analyzed in a comparable way as described above for hSBA titres. Since total IgG is measured as concentration instead of titer, the resulting geometric mean of the concentrations is abbreviated as GMC.

Table 7 LLOQ of total IgG (as measured by ECL) MenACWY indicator strains

Strain	LLOQ	ULOQ
Men A	CCI [redacted]	
Men C		
Men W		
Men Y		

For each N. meningitidis A, C, W and Y and for each (individual response) and all (composite response) serogroup B indicator strain (M14459, M07-0241084*, 96217and NZ98/254) the percentages of subjects with hSBA titres ≥LLOQ and of subjects with 4-fold rise and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated for each study group at each timepoint not previously analyzed. Ninety-five percent (95%) CIs for the difference in percentages between ABCWY (pooled lots) on the one hand and MenB_0_2_6, MenB_0_6, and ACWY groups, respectively, on the other hand, will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

* The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented either in a protocol amendment or in the clinical report.

For each N. meningitidis serogroup A, C, W and Y, analyses of hSBA GMTs, percentages of subjects with hSBA titres ≥LLOQ and of subjects with 4-fold rise, will be repeated by subjects with and without a previous MenACWY vaccination (primed and unprimed). Similarly, analyses of GMCs of the total IgG (as measured by ECL) against serogroups A, C, W and Y will be repeated by subjects with and without a previous MenACWY vaccination (primed and unprimed).

5.4.1.5. Cohen kappa level of agreement

The human serum bactericidal assay (hSBA) and the endogenous complement human serum bactericidal assay (enc-hSBA) provide two different types of results for B strains; the hSBA gives a quantitative, continuous result (hSBA titer) while the enc-hSBA gives a qualitative, categorical result (with/without bactericidal activity).

To assess the agreement between hSBA and enc-hSBA, the Kappa statistics [Cohen, 1960] will be used and the hSBA results will be categorized as follows:

1. The hSBA will be categorized as <LLOQ and ≥LLOQ (Ref. Table 6). Agreement will be assessed versus the positive and negative categories of the enc-hSBA at 1:4 dilution.

To evaluate the strength of the agreement, the following scale [Landis, 1977] will be used:

Table 8 Strength of agreement scale

Kappa	Strength of Agreement
< 0.00	Poor
0.00-0.20	Slight
0.21-0.40	Fair
0.41-0.60	Moderate
0.61-0.80	Substantial
0.81-1.00	Almost Perfect

A 95% Confidence Interval (CI) will be provided together with the point estimate of the Kappa for each of the above situations. The McNemar test will be also performed using the same categorizations of the hSBA results as described above. The aforementioned comparisons/tests will be all performed overall across vaccine groups, separately for each serogroup B test strain. The following SAS code will be used for the Kappa calculation and the McNemar test:

```
PROC FREQ data=dataset;
table assay1_res*assay2_res / agree;
run;
```

where assay1_res represents the enc-hSBA result, assay2_res represents the precategorized hSBA result.

5.4.2. Additional considerations

5.4.2.1. Immunological non-inferiority: MenABCWY vs. rMenB+OMV NZ

As a sensitivity analysis, a parametric model will be run. A generalized linear model with factors for vaccine group and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) will be ran, with the Binary distribution and link function is identity, and outcome is 4-fold rise. If the lower limit of the two-sided 95% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY (pooled) lots –MenB) coming from the model is above -10%, also the sensitivity analysis has demonstrated non-inferiority.

5.4.2.2. Effectiveness by each of the endemic US N. meningitidis serogroup B strains

The SAS code to analyse the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) by strain is specified below. Treatment, and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) will be modelled as fixed effect. To account for a possible over-dispersion, the DSCALE option in the model statement will be evaluated first. The DSCALE will be kept in the model only if the F-statistics for the DSCALE parameter is significant ($p<0.05$). The following SAS code will be used for the VE calculation:

```
ods trace on;
ods output  GEEEmpPEst = genmod_stats
CONVERGENCESTATUS = converge ;

PROC GENMOD data=dataset descending;
class trtgrp region agecat previousACWY;
by strain ;
model outcome = trtgrp region agecat previousACWY / dist= bin link= log
DSCALE alpha=0.05;
estimate 'MenB026-ACWY' trtgrp 1 0 0 0 0 -1/ alpha= 0.05 exp;

/*trtgrp R is MenB0,2,6 and trtgrp W is ACWY*/

run;

ods output close;

data genmod_stats;
set genmod_stats;
by strain ;
where parm = 'trtgrp' and level1 = '1';
rr = exp(estimate);
ub = exp(uppercl);
ve = (1 - rr)*100 ;
ve_ll = (1 - ub) * 100 ;
if ve_ll > 65 then success = 1 ;
else success = 0 ;
run;
```

where outcome represents the Bernoulli distributed outcome without bactericidal activity at a 1:4 dilution (i.e. response is 1 if titre < 4, and 0 if titre ≥ 4), one month after the 3rd vaccination in MenB0,2,6 and one month after the MenACWY vaccination for the ACWY arm, trtgrp indicates the vaccine groups, strain is the serogroup B strain variable, region is either US or ex-US, agecat is the age at enrolment (10-17 YoA or 18-25 YoA), and previousACWY is previous ACWY vaccination (y/n) at enrolment.

rr is the relative risk (RR), which is obtained from the estimated parameters from PROC GENMOD. Vaccine effectiveness (VE) is then derived as (1-rr)x100%.

ub represents the upper bound of the 95% CI of the relative risk. ve_ll is the lower bound of the 95% CI for VE, if the value is greater than 65%, then the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) objective is successful.

In summary in case of convergence issue the following hierarchical decision tree will be applied

- Binary model including region, agecat, and previousACWY

- Binary model, excluding region, agecat, and previousACWY

- Cochran-Mantel-Haenszel (CMH) method (if strain has 100% killed or 0% killed for ANY treatment)

- VE set to 0% (if strain has 100% killed for both treatment)

5.4.2.3. Distribution of percentages of serogroup B invasive disease strains killed

Not applicable

5.4.2.4. Immune response of MenABCWY, rMenB+OMV NZ and MenACWY

Not applicable

5.5. Safety and reactogenicity

5.5.1. Analysis of safety and reactogenicity planned in the protocol

Distribution of subjects by vaccinations will be summarised by vaccine group for the Enrolled Set. In case of vaccination error, subjects will be analyzed “as treated” (according to the vaccine the subject received).

Analysis sets: Solicited Safety Set (solicited local and systemic adverse events and other solicited adverse events), Unsolicited Safety Set (unsolicited adverse events), and Overall Safety Set.

Endpoint	Statistical Analysis Methods
Primary	**Endpoints description**: The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) adverse events during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. All solicited adverse events will be summarised according to defined severity grading scales, see protocol section 12.5.9.3. Frequencies and percentages of subjects experiencing each adverse event will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic adverse event overall and at each time point will also be presented. Post-vaccination solicited adverse events reported from Day 1 to Day 7 will be summarised for the intervals Day 1-3, Day 4-7, and Day 1-7 by maximal severity and by vaccine group, excluding the 30-minute measurement, which will be summarised separately. The severity of solicited local adverse events, including redness (erythema) at injection site, swelling of skin at injection site, and hardness of skin at injection site will be summarised according to categories based on linear measurement: None (1 to 24mm); Mild (25 to 50mm); Moderate (51 to 100mm); Severe (>100mm). Injection site tenderness and systemic reactions (except fever) occurring up to 7 days after each vaccination at Day 1, Day 61 and Day 181 will be summarised according to "mild", "moderate" or "severe". Each solicited local and systemic adverse event will also be further summarised as "none" versus "any" (for fever the latter will be ≥38.0 °C). Use of antipyretics and analgesics will be summarised by frequency by type of use (prophylactic versus treatment) and percentage of subjects reporting use. Body temperature will be summarised 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 temperatures ≥ 38.0 °C and temperatures ≥ 40.0 °C will also be presented.
	Endpoints description: The frequencies and percentages of subjects with any unsolicited ***AEs*** (including all SAEs), ***AEs*** leading to withdrawal and medically attended ***AEs*** during the 7 and the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. The frequencies and percentages of subjects with SAEs, ***AEs*** leading to withdrawal***, AESIs*** and medically attended ***AEs*** throughout the study period. This analysis applies to all adverse events occurring during the study, judged either as possibly related, or not related to vaccination by the investigator, recorded in AE CRF, with a start date on or after the date of first vaccination. AE starting prior to the first vaccination will only be listed. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class. All reported adverse events, as well as adverse events judged by the investigator as possibly related to study vaccine, will be summarised 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 adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted. Separate summaries will be produced for the following categories: • Serious adverse events. • Adverse events that are possibly related to vaccine. • Adverse events of special interest. • Adverse event leading to withdrawal. • Adverse events leading to a medically attended visit. Data listings of all adverse events will be provided by subject. In addition, adverse events in the categories above will be provided as listed data. Local and systemic AEs will be analyzed by point estimates with associated 95% CIs [Clopper, 1934].

5.5.2. Additional considerations

For analyses of the safety and reactogenicity endpoints, subjects will be analyzed "as treated" according to the actual vaccination a subject received.

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

Analyses of safety objectives will be repeated by age group (10-17 years of age and 18-25 years of age), race, sex, region (US/ ex-US), and with and without a previous MenACWY vaccination (primed and unprimed).

A Table and Listing of COVID-19 AE cases will be provided.

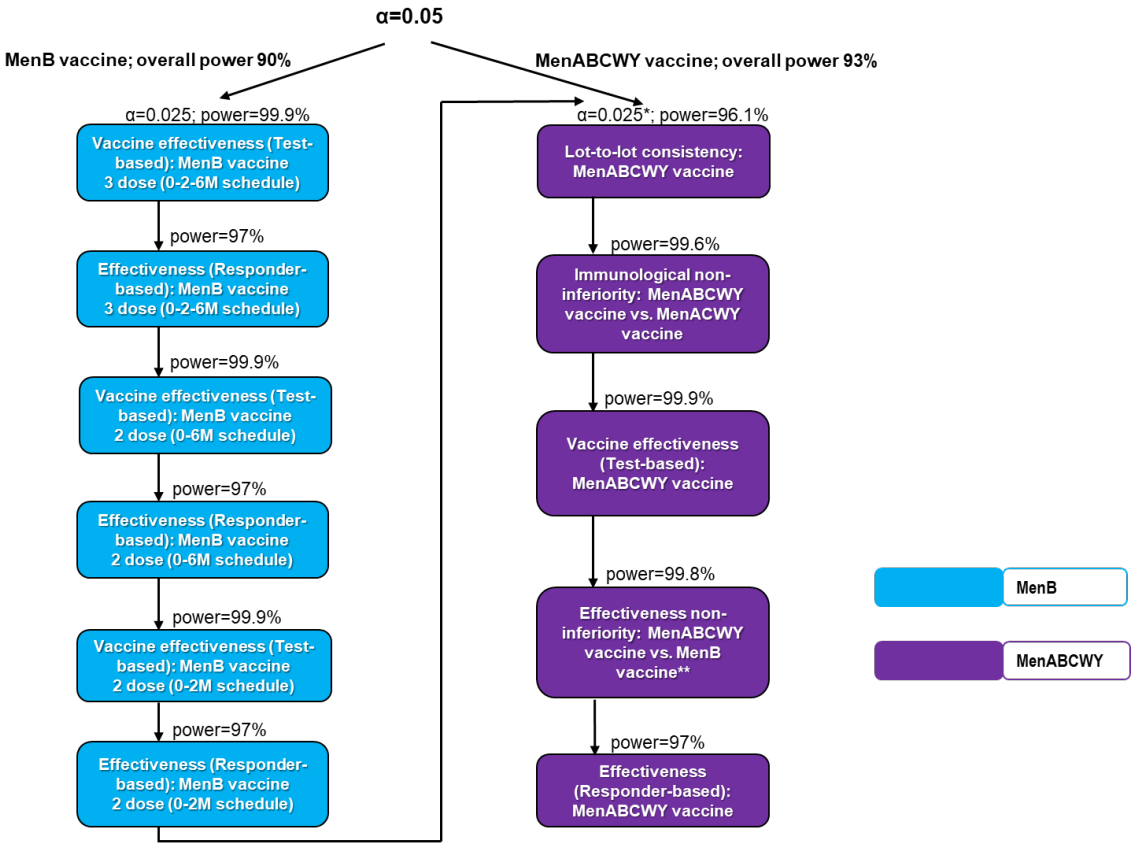
In case for a subject besides ediary data, also solicited reactions were recorded in the CRF, the CRF data will be mapped into the SDTM data with the ediary data (FA domain). For the analysis, the CRF data will be used in case of duplicate data.

6. ANALYSIS INTERPRETATION

Multiple objectives and endpoints require type I error control. Full alpha (0.05) is split equally (alpha=0.025) between rMenB+OMV NZ objectives and MenABCWY objectives. Furthermore, within rMenB+OMV NZ, as well as within MenABCWY, objectives are tested hierarchically. If the first null hypothesis is rejected, then the testing will continue with the second hypothesis at same alpha. Same for 3rd, 4th, and so forth. Whenever a null hypothesis is not rejected, then the testing will stop.

As the comparator for MenABCWY non inferiority objective for the B component will be the selected schedule of rMenB+OMV NZ as determined in this study, the objectives of rMenB+OMV NZ will be analysed first. Additionally, if all null hypotheses related to rMenB+OMV NZ objectives will be rejected, the alpha (alpha=0.025) will be propagated to the MenABCWY part, and hypotheses related to MenABCWY objectives will be tested at full alpha (alpha=0.05). See Figure 2 for an explanation of the hierarchical testing (top to bottom, the order indicated by the arrows).

Figure 2 Hierarchical testing of hypothesis



* Alpha split equally between rMenB+OMV NZ and MenABCWY vaccine objectives.
If all rMenB+OMV NZ objectives achieved, MenABCWY vaccine objectives will be tested at full alpha.
** If all objectives of rMenB+OMV NZ are met, the comparator will be the 0,2-months schedule. If the 0,2-months objective is not met, and the 0,6-months is met, then the 0,6-months schedule will be the comparator. If the 0,6-months is also not met, then the 0,2,6-months schedule will be the comparator.

Refer to Glossary of terms for definitions of test-based and responder-based vaccine effectiveness.

7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

The final study report will contain at least the final analyses of all primary and secondary endpoints.

7.2. Statistical considerations for interim analyses

No interim analysis is planned for this study

8. CHANGES FROM PLANNED ANALYSES

Not applicable

9. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

The following sections describe additional derivation rules and statistical methods which are not presented in section 10.1.

9.1. Data derivation

Not applicable

9.2. Statistical Method

Not applicable

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

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

10.1.1. Attributing events to vaccine doses

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

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

10.1.2. Handling of missing data

10.1.2.1. Dates

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

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

The following exceptions apply:

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

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

10.1.2.2. Laboratory data

Missing laboratory results (including immunological data) will not be replaced.

10.1.2.3. Daily recording of solicited adverse events

10.1.2.3.1. Studies with electronic diaries

For studies using electronic diaries for the collection of solicited adverse events, a solicited adverse events will be considered present only when a daily recording of grade 1 or more is present.

10.1.2.4. Unsolicited adverse events

Unsolicited adverse event summaries are including serious adverse events unless specified otherwise.

Missing severity, relationship with study vaccine, and outcome of unsolicited adverse events will not be replaced and will appear as 'UNKNOWN' in all statistical output.

10.1.3. Data derivation

10.1.3.1. Age at vaccination in days

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

Age = date of vaccination minus date of birth

10.1.3.2. Age at vaccination in months

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

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

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

10.1.3.3. Age at vaccination in years

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

DOB = 10SEP1983, Date of vaccination = 09SEP2018 -> Age = 34 years

DOB = 10SEP1983, Date of vaccination = 10SEP2018 -> Age = 35 years

10.1.3.4. Weight

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

Weight in kilograms = Weight in pounds / 2.2

10.1.3.5. Height

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

Height in centimeters = Height in inches x 2.54

10.1.3.6. Body mass index (BMI)

BMI will be calculated as follows:

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

10.1.3.7. Temperature

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

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

10.1.3.8. Numerical serology results

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

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

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

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

10.1.3.10. Onset day

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

10.1.3.11. Duration of events

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

10.1.3.12. Counting rules for combining solicited and unsolicited adverse events

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

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

10.1.3.13. Counting rules for occurrences of solicited adverse events

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

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with:

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

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

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

10.1.4.2. Differences in percentages

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

10.1.4.3. Demographic/baseline characteristics statistics

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

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

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

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

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

10.1.4.4. Serological summary statistics

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

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

When multiple categories of GMT or GMC values are present in the same table, the number of decimals displayed should match that of the smallest category (i.e. the one with the higher number of decimals). For example, if GMT or GMC values of <0.1

appear in the same table as values of >=0.1 and <10, 3 decimals should be displayed for both.

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

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

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

10.1.5.2. Standardized asymptotic confidence intervals around differences in proportions

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

10.2. TFL TOC

The Tables Figures and Listings (TFL) Table of Contents (TOC) which itemizes the planned list of TFL and their associated lay-out is developed as a separate document.

10.3. Glossary of terms

End of Study (EoS) **(Synonym of End of Trial)**	For studies with collection of human biological samples and/or imaging data, the EoS is defined as Last subject last visit (T10). or Last testing results released of samples collected at Visit 6* * In this case EoS must be achieved no later than 8 months after LSLV.
Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.
Responder-based vaccine effectiveness:	The enc-hSBA methodology involves testing the serum samples from each individual subject against a subset of around 35 strains randomly chosen from the overall panel of 110 meningococcus B US strains. Responder-based vaccine effectiveness is assessed based on the percentage of subjects considered responders, i.e., subjects whose

	serum kills the majority (≥70% in this study) of the tested strains following vaccination.
Test-based vaccine effectiveness:	The enc-hSBA methodology involves testing the serum samples from each individual subject against a subset of around 35 strains randomly chosen from the overall panel of 110 meningococcus B US strains. Test-based vaccine effectiveness is assessed based on the overall percent of individual positive tests following vaccination and represents the reduction in risk compared to the placebo.

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GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A phase III, randomized, controlled, observer-blind study to demonstrate effectiveness, immunogenicity and safety of GSK's meningococcal Group B and combined ABCWY vaccines when administered to healthy adolescents and young adults.
eTrack study number and Abbreviated Title	205416 [MENB REC 2ND GEN-038 (V72_72)]
Scope:	All data pertaining to the above study
Date of Statistical Analysis Plan	Final: 08 Sep 2022

APP 9000058193 Statistical Analysis Plan Template V4 (Effective date: 3June2019)

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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
Eli Type	Internal database code for type of elimination code
ELISA	Enzyme-linked immunosorbent assay
EOS	End of Study
ES	Exposed Set
FAS	Full Analysis Set
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titre
GSK	GlaxoSmithKline
LL	Lower Limit of the confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
PCD	Primary completion Date
PPS	Per-Protocol Set
RR	Relative Risk
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
TFL	Tables Figures and Listings
TOC	Table of Contents

1. DOCUMENT HISTORY

Date	Description	Protocol Version
25 Jul 2019	First version	Amendment 1: 23 MAY 2019
15 Jun 2020	Amendment 1	Amendment 2: 18 MAR 2020
25 Mar 2022	Amendment 2	Amendment 4: 12 MAY 2021
25 Apr 2022	Amendment 3	Amendment 4: 12 MAY 2021
08 Sep 2022	Amendment 4	Amendment 4: 12 MAY 2021

2. OBJECTIVES/ENDPOINTS

Table 1 Study objectives and endpoints

Objectives	Endpoints
Primary	
Vaccine effectiveness (Test-based): rMenB+OMV NZ To demonstrate the effectiveness of the rMenB+OMV NZ vaccine against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity using enc-hSBA at 1 month after the 3-dose (0,2,6-months) and 2-dose (0,6-months; 0,2-months) vaccination series when compared to 1 month after the MenACWY vaccination. *Criterion* *Lower limit (LL) of the two-sided 97.5% confidence interval (CI) for vaccine effectiveness is above 65% against a randomly selected strain panel between the:* • *MenB_0_2_6 and ACWY groups (for 0,2,6-months schedule)* • *MenB_0_6 and ACWY groups (for 0,6-months schedule),* • *MenB_0_2_6 and ACWY groups (for 0,2-months schedule)*	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at 1 month after the: • 3-dose vaccination series in MenB_0_2_6 group (Day 211, Month 7) • 2-dose vaccination series in MenB_0_6 group (Day 211, Month 7), and • 2-dose vaccination series in MenB_0_2_6 group (Day 91, Month 3) • 1 month after the MenACWY vaccination in ACWY group (Day 31, Month 1).
Effectiveness (Responder-based): rMenB+OMV NZ To demonstrate the effectiveness of the rMenB+OMV NZ vaccine by assessing the percentages of subjects whose sera kill ≥70% of strains tested using enc-hSBA at 1 month after the 3-dose (0,2,6-months) and 2-dose (0,6-months; 0,2-months) vaccination series of the rMenB+OMV NZ. *Criterion:* *LL of the two-sided 97.5% CI for the percentages of subjects whose sera kill ≥70% of strains is above 65%, tested for:* • *MenB_0_2_6 group (for 0,2,6-months schedule)* • *MenB_0_6 group (for 0,6-months schedule),* • *MenB_0_2_6 group (for 0,2-months schedule)*	The percentages of subjects whose sera kill ≥70% of the strains tested using enc-hSBA, at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group), • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group)
The 3 vaccine schedules will be tested for both, test-based and responder-based, in a hierarchical way (starting from 0-2-6, to 0-6 and 0-2). Refer to Protocol Section 10.1 for details on continuing the evaluation.	

Objectives	Endpoints
Lot-to-lot consistency: MenABCWY vaccine To demonstrate lot-to-lot consistency of the immune responses of 3 lots of the MenACWY component of the MenABCWY vaccine, as measured by hSBA GMTs directed against serogroups A, C, W and Y at 1 month after last vaccination (0,6-months). *Criterion:* *The two-sided 97.5% CIs^ for the ratio of hSBA GMTs of antibodies against serogroups A, C, W and Y are within the [0.5;2.0] equivalence interval for each pair of lots.*	GMTs directed against serogroups A, C, W and Y for each lot (ABCWY-1 group, ABCWY-2 group, ABCWY-3 group) at 1 month after the last vaccination (Day 211, Month 7)
Immunological non-inferiority: MenABCWY vaccine vs. MenACWY vaccine To demonstrate the immunological non-inferiority of the MenABCWY vaccine compared to the MenACWY vaccine as measured by the percentages of subjects achieving a 4-fold rise in hSBA titres against *N. meningitidis* serogroups A, C, W and Y at 1 month after the last MenABCWY vaccination (0,6-months) and 1 month after the MenACWY vaccination. *Criterion:* *LL of the 2-sided 97.5% CI^ for the group difference in percentages of subjects achieving a 4-fold rise* in hSBA titres is above -10%.*	The percentages of subjects with 4-fold rise* in hSBA titres against *N. meningitidis* serogroups A, C, W and Y at 1 month after the: • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • 1 month after the MenACWY vaccination for the ACWY group (Day 31, Month 1) relative to baseline (Day 1, Month 0).
Vaccine effectiveness (Test-based): MenABCWY vaccine To demonstrate the effectiveness of the MenABCWY vaccine against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains as measured by enc-hSBA at 1 month after the last MenABCWY vaccination (0,6-months) when compared to 1 month after the MenACWY vaccination. *Criterion:* *LL of the two-sided 97.5% CI^ for vaccine effectiveness is above 65% against a randomly selected strain panel between the ABCWY group (pooled lots) and the ACWY group.*	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at 1 month after the: • last vaccination for the ABCWY group (pooled) (Day 211, Month 7), and • 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1).
Effectiveness non-inferiority: MenABCWY vaccine vs. rMenB+OMV NZ vaccine To demonstrate the non-inferiority of the effectiveness of the MenABCWY vaccine (0,6-months schedule) compared to the rMenB+OMV NZ vaccine (0,2,6-months or 0,6-months or 0,2-months)† in terms of percentage of samples with bactericidal serum activity using enc-hSBA against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains. *Criterion:* *LL of the two-sided 97.5% CI^ for the difference in percentages of samples with bactericidal serum activity using enc-hSBA against a randomly selected panel of*	The percentages of samples with bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains at 1 month after the: • last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • 3-dose vaccination series of rMenB+OMV vaccine (Day 211, Month 7 in MenB_0_2_6 group) or 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) or 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group)†

Objectives	Endpoints
endemic US N. meningitidis serogroup B invasive disease strains is above -5% at 1 month after: • *the last vaccination in ABCWY group (pooled lots) (for 0,6 months schedule), and* • *The last vaccination in MenB_0_2_6 group (for 0,2,6-months schedule) or the last vaccination in MenB_0_6 group (for 0,6-months schedule) or the second vaccination in MenB_0_2_6 group (for 0,2-months schedule*	
Effectiveness (Responder-based): MenABCWY vaccine To demonstrate the effectiveness of MenABCWY vaccine by assessing the percentages of subjects whose sera kill ≥70% of strains tested using enc-hSBA at 1 month after the last vaccination of MenABCWY (0,6-months). *Criterion:* *LL of the two-sided 97.5% CI^ for the percentages of subjects whose sera kill ≥70% of strains tested for MenABCWY is above 65%.*	The percentages of subjects whose sera kill ≥70% of the strains tested using enc-hSBA, at 1 month after the last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7).
Safety To evaluate the safety and reactogenicity of the MenB, MenABCWY, and the MenACWY vaccines	• The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [body temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) adverse events (AEs) during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. • The frequencies and percentages of subjects with any unsolicited AEs (including all SAEs, AEs leading to withdrawal, AESIs and medically attended AEs) during the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. • The percentages of subjects with SAEs, AEs leading to withdrawal, AESIs and medically attended AEs throughout the study period [Month 0 to Month 18].
Secondary	
To demonstrate the immunological non-inferiority of the MenABCWY vaccine compared to the rMenB+OMV NZ vaccine as measured by the percentages of subjects achieving a 4-fold rise in hSBA titres against *N. meningitidis* serogroup B indicator strains at 1 month after the last MenABCWY vaccination (0,6-months schedule) and 1 month after the rMenB+OMV NZ vaccination (0,2,6-months or 0,6-months or 0,2-months) † *Criterion:* *Non-inferiority will be demonstrated if the LL of the 2-sided 95% CI for the group difference in percentage of*	The percentages of subjects with 4-fold rise** in hSBA titres against *N. meningitidis* serogroup B indicator strains at 1 month after the: • last MenABCWY vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • 3-dose vaccination series of rMenB+OMV vaccine(Day 211, Month 7 in MenB_0_2_6 group) or 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) or 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group) † relative to baseline (Day 1, Month 0).

Objectives	Endpoints
*subjects achieving a 4-fold rise** in hSBA titres against N. meningitidis serogroup B indicator strains is above -10%.*	
To assess the effectiveness of the rMenB+OMV NZ and MenABCWY vaccines against each of the randomly selected endemic US *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series when compared to 1 month after the MenACWY vaccination.	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group) • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • MenACWY vaccination (Day 31, Month 1 in ACWY group).
To describe the distribution of subjects by percentages of serogroup B invasive disease strains killed using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series of rMenB+OMV NZ and MenABCWY vaccines.	The percentages of serogroup B invasive disease strains killed using enc-hSBA in each subject at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7)
To assess the immune response to the rMenB+OMV NZ (0,2,6-months, 0,6-months and 0,2-months) and MenABCWY (0,6-months) vaccines against *N. meningitidis* serogroup B indicator strains at pre-vaccination (Day 1, Month 0) and at 1 month after the last MenABCWY vaccination and at 1 month after the second and third vaccination of rMenB+OMV NZ.	The immune response to the rMenB+OMV NZ and ABCWY vaccines will be evaluated by measuring bactericidal activity against *N. meningitidis* serogroup B indicator strains as following: *1. The percentages of subjects with hSBA titres ≥ lower limit of quantitation (LLOQ) for each (individual response) and all (composite response) serogroup B indicator strains at baseline (Day 1, Month 0) and at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *2. The percentages of subjects with 4-fold rise** in hSBA titres at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 90, Month 3 in MenB_0_2_6 group), and

Objectives	Endpoints
	• last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *relative to baseline (Day 1, Month 0).* *3. hSBA GMTs at baseline (Day 1, Month 0) and at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *4. hSBA GMRs at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *relative to the baseline (Day 1, Month 0).*
To assess the immune response to MenABCWY (0,6-months schedule) and MenACWY (single dose) vaccines against *N. meningitidis* serogroups A, C, W and Y, at pre-vaccination (Day 1, Month 0) and at 1 month after the first and the last MenABCWY vaccination and 1 month after the MenACWY vaccination.	*1. The percentage of subjects with hSBA titres ≥ LLOQ for serogroups A, C, W and Y at baseline (Day 1, Month 0) and:* • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1). *2. The percentage of subjects with 4-fold rise* in hSBA titres at 1 month after the:* • first vaccination (Day 31, Month 1) for the ABCWY group (pooled lots) compared to the MenACWY vaccination in the ACWY group (Day 31, Month 1) *relative to baseline (Day 1, Month 0).* *3. hSBA GMTs against N. meningitidis serogroups A, C, W and Y* at baseline (Day 1, Month 0) and: • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1). *4.hSBA GMRs against N. meningitidis serogroups A, C, W and Y at:* • 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots) as compared to baseline (Day 1, Month 0), and

Objectives	Endpoints
	• 1 month after the single MenACWY vaccination in the ACWY group (Day 31, Month 1) as compared to baseline (Day 1, Month 0). *5.The total IgG as measured by ELISA GMCs against serogroups A, C, W and Y* at baseline (Day 1, Month 0) and*:* • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1).

Abbreviations: ELISA = enzyme-linked immunosorbent assay; Enc-hSBA = endogenous complement human serum bactericidal assay; GMC = geometric mean concentrations; GMT = geometric mean titre; GMR = geometric mean ratio; CI = confidence interval; hSBA = human serum bactericidal assay; LOD: limit of detection; LLOQ = lower limit of quantitation; LL = lower limit; AE = Adverse event; SAE = Serious adverse event; AESI = Adverse event of special interest

N.meningitidis serogroup B indicator strains = M14459, 96217, M07-0241084 and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively. The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented either in a protocol amendment or in the clinical report.

Refer to Protocol Section 10 for details on evaluation of objectives and sample size justification. Refer to Glossary of terms for definitions of test-based and responder-based effectiveness

^ If the co-primary effectiveness objectives for rMenB+OMV NZ are met, then all objectives for MenABCWY will be evaluated at 95% CI. Refer to Protocol Section 10.1 for details

† If all objectives of rMenB+OMV NZ are met, the comparator will be the 0,2-months schedule. If the 0,2-months objective is not met, and the 0,6-months is met, then the 0,6-months schedule will be the comparator. If the 0,6-months is also not met, then the 0,2,6-months schedule will be the comparator.

*For the Men A, C, W, Y evaluation, the 4-fold rise is defined as:

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

**For the MenB evaluation, the 4-fold rise per each indicator strain is defined as:

- a post-vaccination‡ hSBA titre ≥4 times the LOD for subjects with a pre-vaccination hSBA titre <LOD
- a post-vaccination‡ hSBA titre ≥4 times the LLOQ for subjects with a pre-vaccination hSBA titre ≥LOD and <LLOQ, and
- a post-vaccination‡ hSBA titre ≥4 times the pre-vaccination hSBA titre for subjects with a pre-vaccination hsBA titre ≥LLOQ

‡ = post-2nd vaccination for 0,6 and 0,2 schedule and post-3rd vaccination for 0,2,6 schedule.

3. STUDY DESIGN

3.1. Scientific rationale for study design

As the rMenB+OMV NZ licensure in the US was issued through accelerated approval, the FDA has requested to demonstrate the effectiveness of the vaccine against an extended panel of serogroup B meningococcal strains (MenB) as a post-marketing commitment in US adolescents and young adults, thus confirming that the vaccine can protect against diverse meningococcal B strains prevalent in the United States.

The availability of a pentavalent meningococcal vaccine in a single administration would however reduce the number of injections and could increase coverage for meningococcal disease caused by *N. meningitidis* serogroups A, B, C, W, and Y worldwide. GSK's investigational MenABCWY combination vaccine is intended to protect against 5 of the most prevalent serogroups of *Neisseria meningitidis* (A, B, C, W, Y) in humans.

Hence, along with the licensed MenB vaccine (*Bexsero*), this Phase III study will also assess the safety, effectiveness, and immunogenicity of the investigational MenABCWY vaccine.

Rationale for effectiveness assessment

As mentioned above, one of the primary purposes of this study is to evaluate the effectiveness of 2 or 3 doses of rMenB+OMV NZ and of 2 doses of the MenABCWY vaccines in healthy adolescents and young adults by measuring the bactericidal activity against 110 endemic US *N. meningitidis* serogroup B strains using an endogenous complement human Serum Bactericidal Assay (enc-hSBA). Sera from the ACWY group receiving the MenACWY vaccine will also be tested against serogroup B meningococcal strains by enc-hSBA as a control for test-based effectiveness assessment. The overall vaccine effectiveness (VE) against all 110 strains combined will be computed by means of a generalised linear model. For additional details see statistical analysis section of the Clinical Study Protocol (Protocol Section 10).

Rationale for lot-to-lot consistency assessment

MenABCWY is a reconstituted vaccine with the lyophilised 'ACWY component' and liquid rMenB+OMV NZ. The MenB component has the same formulation as the commercial *Bexsero*. To demonstrate that the lots of the investigational MenABCWY vaccine are adequately representative of the formulation intended for marketing, equivalence will be assessed for 3 different lots of the ACWY component of the ABCWY vaccine.

Rationale for non-inferiority assessment of MenABCWY vs MenACWY and rMenB+OMV NZ

The study aims to also demonstrate that the investigational combination MenABCWY vaccine is not inferior to a licensed MenACWY vaccine (*Menveo*) and a licensed MenB vaccine (*Bexsero*) which are part of the current standards of care in the US for prevention of invasive disease caused by *N. meningitidis* serogroups A, C, W, Y and by *N. meningitidis* serogroup B, respectively.

Rationale for blood volume collected:

In order to provide the necessary serum volume for the bactericidal assays (enc-hSBA and/ or hSBA(s)), 25 mL whole blood will be collected at Visit 2, Visit 4 and Visit 6. At pre-vaccination (Visit 1), 20 mL whole blood will be collected to provide the necessary serum volume for the hSBA.

Blood samples are taken from all subjects irrespective of the testing status in order to maintain the study blind. Refer to Protocol Section 8.4.2.1 for further details.

Rationale for the selected vaccination schedules

rMenB+OMV NZ: This study aims at demonstrating the VE of the rMenB+OMV NZ vaccine administered as 2-dose vaccine, either with a shorter interval (0,2-months) or a prolonged interval (0,6-months) between doses. A 3-dose schedule has been also added to better characterise the VE.

Note: The rMenB+OMV NZ in the ACWY group is administered in a 0,1-months schedule. This interval is within the recommendations in the summary of product characteristics of *Bexsero* and helps in maintaining the blind. No objectives are associated with this schedule of rMenB+OMV NZ.

MenABCWY: A number of different vaccine formulations were evaluated in MenABCWY Phase I and II clinical studies. The formulation with the same active ingredient composition as the rMenB+OMV NZ (*Bexsero*) and MenACWY (*Menveo*) vaccines was chosen as the final formulation of the investigational MenABCWY vaccine. Two doses administered 6 months apart (0,6-months) is considered the optimal dosing schedule, based on serogroup B immunogenicity results from MenABCWY Phase II clinical studies.

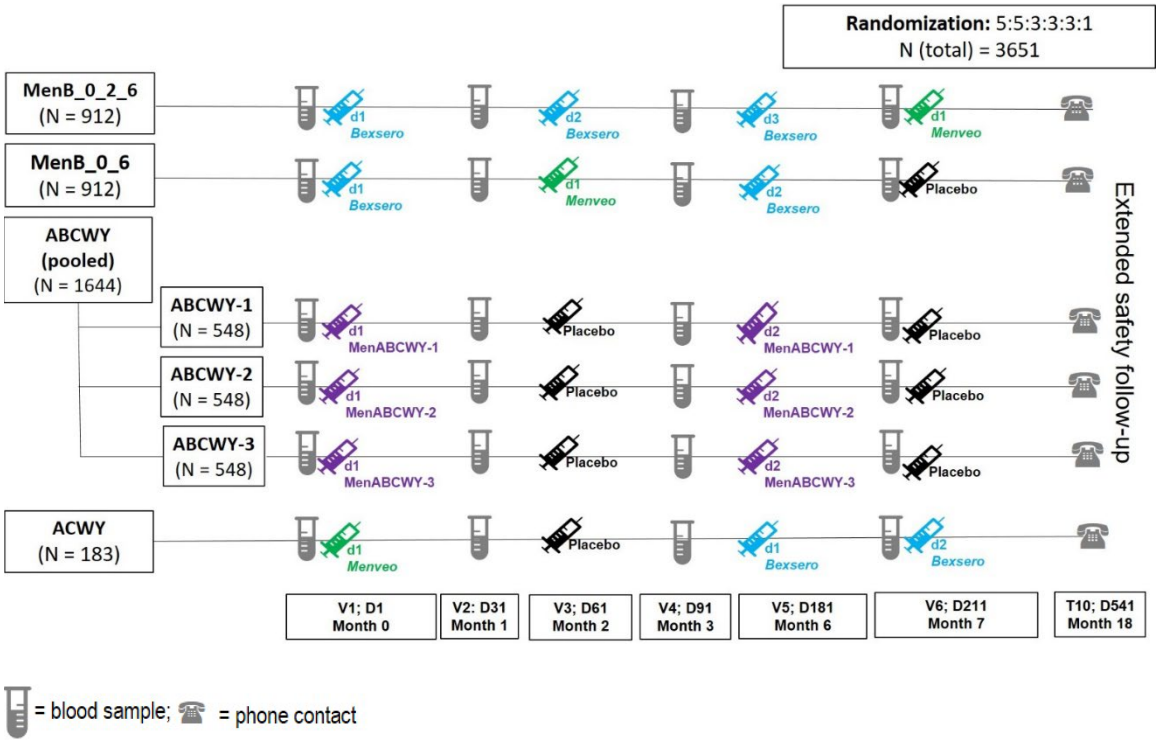
MenACWY: As a comparator for serogroup A, C, W, and Y vaccine effectiveness and immune responses, a single dose of MenACWY vaccine is administered to subjects in the ACWY group. To conform with the standard of care (also in alignment with current ACIP routine immunisation recommendations in US), subjects in the MenB_0_2_6 and MenB_0_6 groups will also receive a dose of MenACWY at Day 211 and Day 61, respectively.

3.1.1. Rationale for the use of placebo

For this study, a placebo (saline solution) will be administered as presented in Figure 1. A placebo is the only available option to minimize possible introduction of reporting bias in collecting information about AEs and to ensure the same number of vaccinations are administered to subjects assigned to either of the six study groups.

3.2. Overall design

Figure 1 Study design overview



N = number of subjects; d = dose; V = visit; D = day; T=Telephone call
Refer to Protocol Table 3 for details on all visits
Note: Home visits may be performed only by sites authorised (as per local regulations and sponsor agreement), with approved site level standard operating procedures (SOP) provided that the compliance with protocol procedures are ensured.

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the schedule of activities (Protocol Section 2), are essential and required for study conduct.

- Type of study: self-contained

- Experimental design: This is a phase III, randomised, controlled, observer-blind, multi-center study to evaluate effectiveness, immunogenicity and safety of rMenB+OMV NZ and MenABCWY vaccines. A total of 3651 healthy adolescents and young adults aged 10-25 years will be enrolled and randomised (5:5:3:3:3:1 ratio) to one of the six parallel study groups:

  – **MenB_0_2_6 group***: subjects will receive 3 doses of rMenB+OMV NZ at Day 1, Day 61 and Day 181 (0, 2 and 0,2,6-months schedule). These subjects will receive 1 dose of the MenACWY vaccine at Day 211**.

  – **MenB_0_6 group**: subjects will receive 2 doses of rMenB+OMV NZ at Day 1 and Day 181 and 1 dose of MenACWY vaccine at Day 61 (rMenB+OMV NZ, 0,6-months schedule). These subjects will receive 1 dose of placebo at Day 211**.

  – **ABCWY-1**: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 1 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211**.

  – **ABCWY-2**: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 2 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211**.

  – **ABCWY-3**: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 3 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211**.

  – **ACWY group**: subjects will receive 1 dose of MenACWY vaccine at Day 1, 1 dose of placebo at Day 61 and 2 doses of rMenB+OMV NZ at Day 181 and Day 211**.

  * MenB_0_2_6 group will also be evaluated for objectives pertaining to 0,2-months vaccination schedule.

  Note 1: A MenB lot will be used for the pre-filled syringe component of the MenABCWY vaccine.

  Note 2: The groups ABCWY-1, ABCWY-2, ABCWY-3 will be pooled into a single group, ABCWY (pooled lots) (except for analysis of lot to lot consistency).

  ** Note 3: In order to let the subjects in MenB_0_2_6 group receive a dose of MenACWY vaccine and for subjects in ACWY group to receive the second dose of rMenB+OMV NZ in line with the vaccine as standard of care (also in line with the Advisory Committee on Immunization Practices (ACIP) recommendations in the US [ACIP, 2011]), the subjects in these groups will receive a vaccination of MenACWY and rMenB+OMV NZ vaccines, respectively, on Day 211 (Visit 6) after completion of the post-vaccination 3 blood sampling. To maintain the blinding of the study, subjects in the rest of the groups (MenB_0_6, ABCWY-1, ABCWY-2 and ABCWY-3) will receive a dose of Placebo. All these vaccines/ product administered at Day 211 are not associated with any study objectives/ endpoints (Safety assessment

conducted after 1 dose of rMenB+OMV NZ in the ACWY group at Day 181 is to maintain the blind of the study).

- Duration of the study: The study duration is approximately 18 months for each subject.
- Primary completion Date (PCD): T10; Day 541.

Refer to Glossary of terms for the definition of PCD.

- End of Study (EoS): the date of release of the last testing results, to be achieved not later than 8 months after Last Subject Last Visit (LSLV) (LSLV = T10; Day 541). If the completion of testing occurs prior the completion of the LSLV the latter date defines the end of study visit.

Refer to Glossary of terms for the definition of EoS.

- Study groups:

Table 2 Study groups and treatment foreseen in the study

Study Groups	Number of subjects	Age (Min-Max)	Treatment name	Vaccine/Product name
MenB_0_2_6	912	10 – 25 y	*Bexsero* (Injection)	rMenB+OMV NZ
			Menveo (Injection)	MenACWY
MenB_0_6	912		*Bexsero* (Injection)	rMenB+OMV NZ
			Menveo (Injection)	MenACWY
			Placebo (Injection)	NaCl
ABCWY-1	548		MenABCWY (with Lot 1 of ACWY) (Injection)	MenABCWY-1
			Placebo (Injection)	NaCl
ABCWY-2	548		MenABCWY (with Lot 2 of ACWY) (Injection)	MenABCWY-2
			Placebo (Injection)	NaCl
ABCWY-3	548		MenABCWY (with Lot 3 of ACWY) (Injection)	MenABCWY-3
			Placebo (Injection)	NaCl
ACWY	183		*Menveo* (Injection)	MenACWY
			Placebo (Injection)	NaCl
			Bexsero (Injection)	rMenB+OMV NZ

Table 3 Overview of study design: Vaccination and Blood Draw Schedule

Visits **Study Day**	**Visit 1** **Day 1**	Visit 2 Day 31	**Visit** 3 **Day 61**	**Visit** 4 **Day 91**	**Visit** 5 **Day 181**	**Visit** 6 **Day 211**
Group **MenB_0_2_6** **N=912**	Pre-vacc Blood sample rMenB+OMV NZ	Post-vacc 1 Blood sample	rMenB+OMV NZ	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample MenACWY
Group **MenB_0_6** **N=912**	Pre-vacc Blood sample rMenB+OMV NZ	Post-vacc 1 Blood sample	MenACWY	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample Placebo
Group **ABCWY-1** **N=548**	Pre-vacc Blood sample MenABCWY-1	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-1	Post-vacc 3 Blood sample Placebo
Group **ABCWY-2** **N=548**	Pre-vacc Blood sample MenABCWY-2	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-2	Post-vacc 3 Blood sample Placebo
Group **ABCWY-3** **N=548**	Pre-vacc Blood sample MenABCWY-3	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-3	Post-vacc 3 Blood sample Placebo
Group **ACWY** **N=150**	Pre-vacc Blood sample MenACWY	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample rMenB+OMV NZ

N = number of subjects; Pre-vacc = pre-vaccination; Post-vacc = post-vaccination

- Treatment allocation: At Day 1, prior to the study vaccination, subjects will be randomised to 1 of the 6 study groups according to a 5:5:3:3:3:1 ratio.
- Blinding: Observer-blind. Kindly refer to Protocol Section 7.3 for details on blinding and unblinding procedures.
- Sampling schedule:
  - A total of 4 blood samples* will be collected from each subject at Day 1 (pre-vaccination blood sample; approximately 20 mL), at Day 31 (post-vaccination 1 blood sample; approximately 25 mL), at Day 91 (post-vaccination 2 blood sample; approximately 25 mL) and at Day 211 (post-vaccination-3 blood sample; approximately 25 mL).
  - Urine sampling: Urine samples for pregnancy testing will be collected from female subjects of child-bearing potential at Visit 1 (Day 1), Visit 3 (Day 61), Visit 5 (Day 181) and Visit 6 (Day 211) prior to the vaccination.

  * Insufficient blood volume may lead to test cancellation and jeopardise the statistical power. Hence, every effort must be done to collect blood volume as per protocol requirements.
- Data collection: standardised Electronic Case Report Form (eCRF). Solicited symptoms will be collected using a subject Diary (electronic Diary [eDiary]).
- Safety monitoring: Regular safety follow-up will be done through telephone calls (T). There will also be an extended safety follow-up (ESFU) phone call 12 months post-vaccination 3 (Day 181; Visit 5). This ESFU phone call will also mark the study conclusion. Refer to Protocol Table 3 and Protocol Section 8.5.3 for details on the safety follow-up.

3.3. Number of subjects

A total of 3651 subjects will be randomised in a ratio of 5:5:3:3:3:1; 912 each in MenB_0_2_6 and MenB_0_6 groups, 548 in each ABCWY groups and 183 in ACWY group. Assuming a 25% drop out rate, this should provide approximately 684 evaluable subjects in each of the MenB groups, 411 evaluable subjects in each of the ABCWY groups and 137 evaluable subjects in the ACWY group.

Refer to Protocol Section 10.1 for a detailed description of the criteria used in the determination of sample size.

Withdrawals will not be replaced.

3.4. Subject and study completion

A subject is considered to have completed the study, if the subject is available for the concluding contact (T10; Day 541) as described in the protocol.

Global completion of the study is required in order to provide enough subjects as defined in Protocol Section 10.1 Sample Size Determination.

4. ANALYSIS SETS

4.1. Definition

For purposes of analysis, the following analysis sets are defined:

4.1.1. Enrolled Set

Subject/ Subject for whom parent(s)/LAR's agreed to participate in a clinical study after completion of the informed consent process, who meet screening/eligibility criteria and randomized and/or received study intervention or undergone an invasive procedure.

4.1.2. Exposed Set

All subjects who received at least 1 dose of the study treatment. The allocation in a group is done in function of all administered treatments.

4.1.3. Full Analysis Set

All subjects who received at least 1 dose of the study treatment and have post-vaccination effectiveness or immunogenicity data.

4.1.4. Per Protocol Set

All subjects in the Full Analysis Set minus subjects with protocol deviations that lead to exclusion from the Per Protocol Set.

4.1.5. Solicited Safety Set

All subjects who received at least 1 dose of the study treatment (Exposed Set) who have solicited safety data beyond 30 minutes post vaccination.

4.1.6. Unsolicited Safety Set

All subjects who received at least 1 dose of the study treatment (Exposed Set) that report unsolicited AEs/report not having unsolicited AEs.

4.1.7. Overall Safety Set

All subjects that belong to the Unsolicited safety or/and to the Solicited safety set.

4.2. Criteria for eliminating data from Analysis Sets

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

4.2.1. Elimination from Exposed Set (ES)

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

4.2.2. Elimination from Per protocol Set (PPS)

4.2.2.1. Excluded subjects

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

Table 4 Elimination code and condition to exclude a subject from the PPS analysis

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
800	Fraudulent data	All	All
900	Invalid informed consent	All	All
1030	Study vaccine not administered at all	All	All
1050	Randomization failure	Visit 1, 3, 5	All
1060	Randomization code was broken	All	All
1070.1	Subjects got vaccinated with the correct vaccine but containing a lower volume	Visit 1, 3, 5	All
1070.2	Vaccination not according to protocol	Visit 1, 3, 5	All
1080	Vaccine temperature deviation	Visit 1, 3, 5	All
1090	Expired vaccine administered	Visit 1, 3, 5	All
1500.1	Other deviation from study procedures not able to classified under any other categories	All	All
1500.2	Any other GCP non-compliance not able to classified under any other categories	All	All
2010	Protocol violation (inclusion/exclusion criteria)	All	All
2040	Administration of any medication forbidden by the protocol	Visit 1, 3, 5	All
2050	Not withdrawn after developing withdrawal criteria other than prohibited concomitant vaccination/medication (medical condition forbidden)	All	All
2060	Concomitant infection related to the vaccine which may influence immune response (only meningococcal infection)	All	All
2080	Subjects did not comply with vaccination schedule	Visit 3, 5	All

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
2090	Subjects did not comply with blood sample schedule	Visit 2, 4, 6	All
2100	Serological results not available post-vaccination for all tests	Visit 2, 4, 6	All
2120	Obvious incoherence or abnormality or error in data related to testing	Visit 2, 4, 6	All
2130	Biological sample specimen procedures not compliant with protocol	Visit 2, 4, 6	All

4.2.3. Elimination from unsolicited and solicited safety set

4.2.3.1. Excluded subjects

4.2.3.1.1. Unsolicited safety set

Code 1030 (Study vaccine not administered at all), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1150 (no post-vaccination safety data) will be used for identifying subjects eliminated from the unsolicited safety set.

4.2.3.1.2. Solicited safety set

Code 1030 (Study vaccine not administered at all), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1160 (no post-vaccination solicited safety data) will be used for identifying subjects eliminated from the solicited safety set.

5. STATISTICAL ANALYSES

Standard data derivation rules and statistical methods are described in section 10.1 while the study specific data derivation rules and stat methods are described in section 9.

5.1. Disposition of subjects

5.1.1. Analysis of disposition of subjects planned in the protocol

Number of subjects enrolled, vaccinated subjects (at least 1 vaccination, full vaccination course), reason for early withdrawal, FAS, and PPS will be described by vaccine group.

5.1.2. Additional considerations

Not applicable

5.2. Demography and baseline characteristics analyses

5.2.1. Analysis of demography and baseline characteristics planned in the protocol

Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age, height, weight, and body mass index (BMI) at enrolment will be calculated overall and by vaccine group.

Distributions of subjects by sex, race, ethnic origin will be summarised overall and by vaccine group.

5.2.2. Additional considerations

A summary table of important protocol deviations related to COVID-19 will be provided. Also, a listing will be produced.

5.3. Primary effectiveness and immunogenicity

5.3.1. Analysis of primary effectiveness and immunogenicity planned in the protocol

Refer to Glossary of terms for definitions of test-based and responder-based vaccine effectiveness. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then all objectives for MenABCWY will be evaluated at 95% CI (Sections 5.3.1.7 through 5.3.1.11, ref Protocol Section 10.1).

5.3.1.1. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Analysis set: Per-protocol set (PPS) will be the primary analysis population

Statistical method: The VE is defined as 1- RR= (1- percentage of samples without bactericidal serum activity at 1:4 dilution in MenB group / percentage of samples without bactericidal serum activity at 1:4 dilution in the ACWY group) x100% and it will be analyzed using a generalised linear model with vaccine group, strain, and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) as independent variables. Furthermore, a repeated statement will be used to estimate the variance of the RR including correlation within subject's responses to different strains. If the statistical model does not converge due to (one of) the factor(s), a model without this/these factor(s) will be fitted instead. The response variable of the model will be the Bernoulli distributed outcome without bactericidal activity at a 1:4 dilution (i.e. response is 1 if titre < 4, and 0 if titre ≥ 4), at 1 month after the last vaccination (Month 7) in the MenB group and at Month 1 for the ACWY group. Each subject will contribute with approximately 35 measures to this analysis, each of the measures corresponding to the response variable to one of the 35 strains randomly assigned to be tested with the samples available for that specific subject.

In order to obtain the VE measure which is a measure based on the relative risk (RR), a generalised linear model will be used with the Binary distribution and link function log in order to compute the log RR and the corresponding 97.5% CI. The obtained values will be exponentiated to obtain the RR and the corresponding 97.5% CI. The VE will be computed as 100% x (1 – RR). Effectiveness of rMenB+OMV NZ (0,2,6-months schedule) will be demonstrated if the lower limit of the two-sided 97.5% CI for VE between MenB and the ACWY group is above 65%.

5.3.1.2. Effectiveness (Responder-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Analysis set: FAS will be the primary analysis population.

Statistical method: The percentage of responders (see definition in Glossary of terms) and the corresponding exact two-sided 97.5% CI based on Clopper-Pearson method will be calculated [Clopper, 1934].

The objective is to demonstrate that the lower limit of the 97.5% CI for the percentage of responders is higher than 65%.

5.3.1.3. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 5.3.1.1

5.3.1.4. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 5.3.1.2

5.3.1.5. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 5.3.1.1

5.3.1.6. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 5.3.1.2

5.3.1.7. Lot-to-lot consistency: MenABCWY - ACWY component

Analysis set: The analysis of lot-to-lot consistency will be based on the PPS.

Statistical method: For each of the three ABCWY lots (Lots 1, 2 and 3 of the MenACWY component of the ABCWY vaccine), GMTs and 97.5% CIs will be calculated by exponentiating (base 10) the least squares means and the lower and upper limits of the 97.5% CIs of the log transformed titres (base10) obtained from an Analysis of Variance

(ANOVA) with factors for vaccine lot and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)). Additionally, lot-to-lot GMT ratios will be computed for each pair of ABCWY lots. Ninety-seven point five percent (97.5%) CIs for the ratios of GMTs will be constructed by exponentiating the difference of the least square means of the log transformed titres and the lower and upper limits of the 97.5% CIs on the difference obtained from the ANOVA model above.

Lot-to-lot consistency criterion: The three ABCWY lots will be considered equivalent if for each of the 4 serogroups A, C, W and Y and each pair of vaccine lots, the two-sided 97.5% CI on the ratio of GMTs at 1 month after the last vaccination will be contained within the interval [0.5, 2.0].

If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.1.8. Immunological non-inferiority: MenABCWY vs. MenACWY

Analysis set: PPS restricted to subjects without previous ACWY vaccination will be the primary analysis population.

Statistical method: The percentage of subjects with 4-fold rise* in hSBA titres against MenACWY indicator strains A, C, W and Y and the corresponding exact two-sided 97.5% CIs based on Clopper-Pearson method will be calculated for the ABCWY (pooled lots) group and the ACWY group [Clopper, 1934]. The 97.5% CIs for the difference in percentages between ABCWY (pooled lots) and ACWY group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-Inferiority criterion: Non-inferiority of MenABCWY vaccine for the proportion of subjects with 4-fold rise will be demonstrated if the lower limit of the two-sided 97.5% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY (pooled) lots –ACWY) is above -10%.

* For the Men A, C, W, Y evaluation, the 4-fold rise is defined as:

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

Table 5 reads the LOD and LLOQ of MenACWY indicator strains used in the definition of 4-fold rise provided by the laboratory.

Table 5 LOD and LLOQ of MenACWY indicator strains

Strain	LOD	LLOQ
Men A (3125)	CCI [redacted]	
Men C (C11)		
Men W (240070)		
Men Y (860800)		

If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.1.9. Vaccine effectiveness (Test-based): MenABCWY

See Section 5.3.1.1. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the VE for MenABCWY will be evaluated at 95% CI.

5.3.1.10. Effectiveness non-inferiority: MenABCWY vs. rMenB+OMV NZ

Analysis set: PPS will be the primary analysis population.

Statistical method: The percentage of samples with bactericidal activity measured by enc-hSBA at 1:4 dilution and the corresponding exact two-sided 97.5% CIs based on Clopper-Pearson method will be calculated for the ABCWY (pooled lots) group and the MenB group comparator that will be selected (ref: the footnote of Figure 2). The 97.5% CIs for the difference in percentages between ABCWY (pooled lots) and selected MenB group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-Inferiority criterion: Non-inferiority of MenABCWY vaccine for the percentage of samples with bactericidal activity measured by enc-hSBA at 1:4 dilution will be demonstrated if the lower limit of the two-sided 97.5% CI for the difference between the 2 groups (ABCWY (pooled) lots – MenB) is above -5%.

If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.1.11. Effectiveness (Responder-based): MenABCWY

See Section 5.3.1.2. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the effectiveness (responder-based) for MenABCWY will be evaluated at 95% CI.

5.3.2. Additional considerations

Analyses of the primary effectiveness and immunogenicity objectives will be repeated by age group (10-17 years of age and 18-25 years of age), race, sex, region (US/ ex-US), and subjects with and without a previous MenACWY vaccination (primed and unprimed).

5.3.2.1. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

The SAS code to analyse the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) objective is specified below. Treatment, region, age category, previous ACWY vaccination, and strains will be modelled as fixed effect. To account for a possible over-dispersion, the DSCALE option in the model statement will be evaluated first. The DSCALE will be kept in the model only if the F-statistics for the DSCALE parameter is significant ($p<0.05$). The following SAS code will be used for the VE calculation:

```
ods trace on;
ods output GEEEmpPEst = genmod_stats
CONVERGENCESTATUS = converge ;

PROC GENMOD data=dataset descending;
class trtgrp strain region agecat previousACWY subject_id ;
model outcome = trtgrp strain region agecat previousACWY / dist= bin
link= log DSCALE;
repeated subject = subject_id / type= CS withinsubject= strain;
estimate 'MenB026-ACWY' trtgrp 1 0 0 0 0 -1/ alpha=0.025 exp;

/*trtgrp R is MenB0,2,6 and trtgrp W is ACWY*/

run;

ods output close;

data genmod_stats;
set genmod_stats;
where parm = 'trtgrp' and level1 = '1';
rr = exp(estimate);
ub = exp(uppercl);
ve = (1 - rr)*100 ;
ve_ll = (1 - ub) * 100 ;
if ve_ll > 65 then success = 1 ;
else success = 0 ;
run;
```

where outcome represents the Bernoulli distributed outcome without bactericidal activity at a 1:4 dilution (i.e. response is 1 if titre < 4, and 0 if titre ≥ 4), one month after the 3rd vaccination in MenB 0,2,6 and one month after the MenACWY vaccination for the ACWY arm, trtgrp indicates the vaccine groups, strain is the serogroup B strain variable, region is either US or ex-US, agecat is the age at enrolment (10-17 YoA or 18-25 YoA), and previousACWY is previous ACWY vaccination (y/n) at enrolment.

rr is the relative risk (RR), which is obtained from the estimated parameters from PROC GENMOD. Vaccine effectiveness (VE) is then derived as (1-rr)x100%.

ub represents the upper bound of the 97.5% CI of the relative risk. ve_ll is the lower bound of the 97.5% CI for VE, if the value is greater than 65%, then the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) objective is successful.

5.3.2.2. Effectiveness (Responder-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Not applicable

5.3.2.3. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 5.3.2.1, with the difference in the treatment arm:

```
PROC GENMOD data=dataset descending;
class trtgrp strain region agecat previousACWY subject_id ;
model outcome = trtgrp strain region agecat previousACWY / dist= bin
link= log DSCALE ;
repeated subject = subject_id / type= CS withinsubject= strain ;
estimate 'MenB06-ACWY' trtgrp 0 1 0 0 0 -1/ alpha=0.025 exp;

/*trtgrp S is MenB0,6 and trtgrp W is ACWY*/

run;
```

5.3.2.4. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

Not applicable

5.3.2.5. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 5.3.2.1, with the difference the outcome data for group R is from one month after the 2nd vaccination instead of one month after the 3rd vaccination.

5.3.2.6. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

Not applicable

5.3.2.7. Lot-to-lot consistency: MenABCWY - ACWY component

Not applicable

5.3.2.8. Immunological non-inferiority: MenABCWY vs. MenACWY

As a sensitivity analysis, a parametric model will be run. A generalized linear model with factors for vaccine group and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA)) will be ran, with the Binary distribution and link function is identity, and outcome is 4-fold rise. If the lower limit of the two-sided 97.5% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY (pooled) lots –ACWY) coming from the model is above -10%, also the sensitivity analysis has demonstrated non-inferiority. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.2.9. Vaccine effectiveness (Test-based): MenABCWY

See Section 5.3.2.1, with the difference in the estimate statement:

```
PROC GENMOD data=dataset descending;
class trtgrp strain region agecat previousACWY subject_id ;
model outcome = trtgrp strain region agecat previousACWY / dist= bin
link= log DSCALE ;
repeated subject = subject_id / type= CS withinsubject= strain ;
estimate ' MenABCWY-ACWY' trtgrp 0 0 1 1 1 -3/ alpha=0.025 exp
divisor=3;

/*trtgrp T, U, and V are the ABCWY-1, ABCWY-2, and ABCWY-3 lots and
trtgrp W is ACWY*/
run;
```

5.3.2.10. Effectiveness non-inferiority: MenABCWY vs. rMenB+OMV NZ

As a sensitivity analysis, a parametric model will be run. A generalized linear model with factors for vaccine group and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) will be ran, with the Binary distribution and link function is identity, and outcome is bactericidal activity measured by enc-hSBA at 1:4 dilution. If the lower limit of the two-sided 97.5% CI for the difference in percentage of samples with bactericidal activity measured by enc-hSBA at 1:4 dilution between the 2 groups (ABCWY (pooled) lots –MenB) coming from the model is above -5%, also the sensitivity analysis has demonstrated non-inferiority. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

In addition to the comparison of MenABCWY vs the selected MenB schedule per Section 5.3.1.10, MenABCWY will be compared to the other MenB schedule/schedules, whichever is applicable in the same way as described in Section 5.3.1.10. If MenB 0,2 schedule is selected as comparator, in addition MenABCWY will be compared to Menb 0,6 and MenB 0,2,6 schedule. If MenB 0,6 schedule is selected as comparator, in addition MenABCWY will be compared to MenB 0,2,6 schedule. No success criterion is defined for these group comparisons.

5.3.2.11. Effectiveness (Responder-based): MenABCWY

Not applicable

5.4. Secondary effectiveness and immunogenicity

5.4.1. Analysis of secondary effectiveness and immunogenicity planned in the protocol

5.4.1.1. Immunological non-inferiority: MenABCWY vs. rMenB+OMV NZ

Analysis set: PPS will be the primary analysis population.

Statistical method: The percentages of subjects with 4-fold rise** in hSBA titres against N. meningitidis serogroup B indicator strains (M14459, 96217, M07-0241084* and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively) at 1 month after the last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) and 1 month after the 3-dose vaccination series (Day 211, Month 7) in MenB_0_2_6 group or 2-dose vaccination series (Day 211, Month 7) in MenB_0_6 group or 2-dose vaccination series (Day 91, Month 3) in MenB_0_2_6 group and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated [Clopper, 1934]. The 95% CIs for the difference in percentages between ABCWY group (pooled lots) and MenB_0_2_6 group and MenB_0_6 group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-inferiority criterion: Non-inferiority of MenABCWY vaccine for the proportion of subjects with 4-fold rise will be demonstrated if the lower limit of the 2-sided 95% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY group (pooled lots) –selected MenB group) is above -10%.

* The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented either in a protocol amendment or in the clinical report.

** For the MenB evaluation, the 4-fold rise per each indicator strain is defined as:

- a post-vaccination‡ hSBA titre ≥4 times the LOD for subjects with a pre-vaccination hSBA titre <LOD
- a post-vaccination‡ hSBA titre ≥4 times the LLOQ for subjects with a pre-vaccination hSBA titre ≥LOD and <LLOQ, and
- a post-vaccination‡ hSBA titre ≥4 times the pre-vaccination hSBA titre for subjects with a pre-vaccination hSBA titre ≥LLOQ

‡ = post-2nd vaccination for 0,6 and 0,2 schedule and post-3rd vaccination for 0,2,6 schedule).

Table 6 reads the LOD and LLOQ of hSBA titres against N. meningitidis serogroup B indicator strains used in the definition of 4-fold rise provided by the laboratory.

Table 6 LOD and LLOQ of hSBA titres against N. meningitidis serogroup B indicator strains

Strain	LOD	LLOQ
NZ98-254	CCI [redacted]	
96217		
M14459		
M13520		

5.4.1.2. Effectiveness by each of the endemic US N. meningitidis serogroup B strains

Analysis set: FAS will be the primary analysis population. The ABCWY (pooled lots) group and the MenB group comparator that will be selected (ref: the footnote of Figure 2) will be used for the purpose of this analysis.

Statistical method: The VE per strain will be calculated as described in Section 5.3.1.1, using a generalised linear model with vaccine group, and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) as independent variables, and alpha=0.05 leading to 95% CI. In case for a strain 100% response will be observed in both vaccine groups, VE against these strain will be assessed by calculating 95% CI for relative risk from raw proportions, and VE=1-RR.

5.4.1.3. Distribution of percentages of serogroup B invasive disease strains killed

Analysis set: FAS will be the primary analysis population. The ABCWY (pooled lots) group and the MenB group comparator that will be selected (ref: the footnote of Figure 2) will be used for the purpose of this analysis.

Statistical method: Summary statistics of the percentage of serogroup B invasive disease strains killed within a subject using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series of rMenB+OMV NZ and MenABCWY vaccines.

Summary statistics and 95% CI for the mean percentage will be presented, as well as a Figure of the cumulative distribution function.

5.4.1.4. Immune response of MenABCWY, rMenB+OMV NZ and MenACWY

Analysis set: The analysis will be based on the FAS.

Statistical method: The hSBA titres at each time point for all groups (ABCWY group (pooled lots), MenB_0_2_6 and MenB_0_6 groups) will be logarithmically transformed (base10) to fulfil the normal distribution assumption. For each N. meningitidis serogroup A, C, W and Y and each B indicator strain (M14459, 96217, M07-0241084* and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively), the GMTs and GMRs (post-vaccination/baseline) will be obtained from an Analysis of Variance (ANOVA) with factors for vaccine group, region (US/ex-US), age category (10-17 YoA/18-25 YoA), and previous MenACWY vaccination (y/n), and then exponentiating the log-transformed means and their 95% CIs. The ratio of GMTs and GMRs between two groups and the corresponding CI will be estimated additionally.

The total IgG (as measured by ECL) against serogroups A, C, W and Y at baseline (Day 1, Month 0) and

- at 1 month after the first (Day 31, Month 1) and the last vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and
- at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1),

will be analyzed in a comparable way as described above for hSBA titres. Since total IgG is measured as concentration instead of titer, the resulting geometric mean of the concentrations is abbreviated as GMC.

Table 7 LLOQ of total IgG (as measured by ECL) MenACWY indicator strains

Strain	LLOQ
Men A	CCI [redacted]
Men C	
Men W	
Men Y	

For each N. meningitidis A, C, W and Y and for each (individual response) and all (composite response) serogroup B indicator strain (M14459, M07-0241084*, 96217and NZ98/254) the percentages of subjects with hSBA titres ≥LLOQ and of subjects with 4-fold rise and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated for each study group at each timepoint not previously analyzed. Ninety-five percent (95%) CIs for the difference in percentages between ABCWY (pooled lots) on the one hand and MenB_0_2_6, MenB_0_6, and ACWY groups, respectively, on the other hand, will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

* The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented either in a protocol amendment or in the clinical report.

5.4.2. Additional considerations

5.4.2.1. Immunological non-inferiority: MenABCWY vs. rMenB+OMV NZ

As a sensitivity analysis, a parametric model will be run. A generalized linear model with factors for vaccine group and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) will be ran, with the Binary distribution and link function is identity, and outcome is 4-fold rise. If the lower limit of the two-sided 95% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY (pooled) lots –MenB) coming from the model is above -10%, also the sensitivity analysis has demonstrated non-inferiority.

5.4.2.2. Effectiveness by each of the endemic US N. meningitidis serogroup B strains

The SAS code to analyse the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) by strain is specified below. Treatment, and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) will be modelled as fixed effect. To account for a possible over-dispersion, the DSCALE option in the model statement will be evaluated first. The DSCALE will be kept in the model only if the F-statistics for the DSCALE parameter is significant ($p<0.05$). The following SAS code will be used for the VE calculation:

```
ods trace on;
ods output  GEEEmpPEst = genmod_stats
CONVERGENCESTATUS = converge ;

PROC GENMOD data=dataset descending;
class trtgrp region agecat previousACWY;
by strain ;
model outcome = trtgrp region agecat previousACWY / dist= bin link= log
DSCALE alpha=0.05;
estimate 'MenB026-ACWY' trtgrp 1 0 0 0 0 -1/ alpha= 0.05 exp;

/*trtgrp R is MenB0,2,6 and trtgrp W is ACWY*/

run;

ods output close;

data genmod_stats;
set genmod_stats;
by strain ;
where parm = 'trtgrp' and level1 = '1';
rr = exp(estimate);
ub = exp(uppercl);
ve = (1 - rr)*100 ;
ve_ll = (1 - ub) * 100 ;
if ve_ll > 65 then success = 1 ;
else success = 0 ;
run;
```

where outcome represents the Bernoulli distributed outcome without bactericidal activity at a 1:4 dilution (i.e. response is 1 if titre < 4, and 0 if titre ≥ 4), one month after the 3rd vaccination in MenB0,2,6 and one month after the MenACWY vaccination for the ACWY arm, trtgrp indicates the vaccine groups, strain is the serogroup B strain variable, region is either US or ex-US, agecat is the age at enrolment (10-17 YoA or 18-25 YoA), and previousACWY is previous ACWY vaccination (y/n) at enrolment.

rr is the relative risk (RR), which is obtained from the estimated parameters from PROC GENMOD. Vaccine effectiveness (VE) is then derived as (1-rr)x100%.

ub represents the upper bound of the 95% CI of the relative risk. ve_ll is the lower bound of the 95% CI for VE, if the value is greater than 65%, then the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) objective is successful.

In summary in case of convergence issue the following hierarchical decision tree will be applied

- Binary model including region, agecat, and previousACWY

- Binary model, excluding region, agecat, and previousACWY

- Cochran-Mantel-Haenszel (CMH) method (if strain has 100% killed or 0% killed for ANY treatment)

- VE set to 0% (if strain has 100% killed for both treatment)

5.4.2.3. Distribution of percentages of serogroup B invasive disease strains killed

Not applicable

5.4.2.4. Immune response of MenABCWY, rMenB+OMV NZ and MenACWY

Not applicable

5.5. Safety and reactogenicity

5.5.1. Analysis of safety and reactogenicity planned in the protocol

Distribution of subjects by vaccinations will be summarised by vaccine group for the Enrolled Set. In case of vaccination error, subjects will be analyzed "as treated" (according to the vaccine the subject received).

Analysis sets: Solicited Safety Set (solicited local and systemic adverse events and other solicited adverse events), Unsolicited Safety Set (unsolicited adverse events), and Overall Safety Set.

Endpoint	Statistical Analysis Methods
Primary	**Endpoints description**: The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) adverse events during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. All solicited adverse events will be summarised according to defined severity grading scales, see protocol section 12.5.9.3. Frequencies and percentages of subjects experiencing each adverse event will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic adverse event overall and at each time point will also be presented. Post-vaccination solicited adverse events reported from Day 1 to Day 7 will be summarised for the intervals Day 1-3, Day 4-7, and Day 1-7 by maximal severity and by vaccine group, excluding the 30-minute measurement, which will be summarised separately. The severity of solicited local adverse events, including redness (erythema) at injection site, swelling of skin at injection site, and hardness of skin at injection site will be summarised according to categories based on linear measurement: None (1 to 24mm); Mild (25 to 50mm); Moderate (51 to 100mm); Severe (>100mm). Injection site tenderness and systemic reactions (except fever) occurring up to 7 days after each vaccination at Day 1, Day 61 and Day 181 will be summarised according to "mild", "moderate" or "severe". Each solicited local and systemic adverse event will also be further summarised as "none" versus "any" (for fever the latter will be ≥38.0 °C). Use of antipyretics and analgesics will be summarised by frequency by type of use (prophylactic versus treatment) and percentage of subjects reporting use. Body temperature will be summarised 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 temperatures ≥ 38.0 °C and temperatures ≥ 40.0 °C will also be presented.
	Endpoints description: The frequencies and percentages of subjects with any unsolicited ***AEs*** (including all SAEs), ***AEs*** leading to withdrawal and medically attended ***AEs*** during the 7 and the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. The frequencies and percentages of subjects with SAEs, ***AEs*** leading to withdrawal***, AESIs*** and medically attended ***AEs*** throughout the study period. This analysis applies to all adverse events occurring during the study, judged either as possibly related, or not related to vaccination by the investigator, recorded in AE CRF, with a start date on or after the date of first vaccination. AE starting prior to the first vaccination will only be listed. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class. All reported adverse events, as well as adverse events judged by the investigator as possibly related to study vaccine, will be summarised 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 adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted. Separate summaries will be produced for the following categories: • Serious adverse events. • Adverse events that are possibly related to vaccine. • Adverse events of special interest. • Adverse event leading to withdrawal. • Adverse events leading to a medically attended visit. Data listings of all adverse events will be provided by subject. In addition, adverse events in the categories above will be provided as listed data. Local and systemic AEs will be analyzed by point estimates with associated 95% CIs [Clopper, 1934].

5.5.2. Additional considerations

For analyses of the safety and reactogenicity endpoints, subjects will be analyzed "as treated" according to the actual vaccination a subject received.

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

Analyses of safety objectives will be repeated by age group (10-17 years of age and 18-25 years of age), race, sex, region (US/ ex-US), and with and without a previous MenACWY vaccination (primed and unprimed).

A Table and Listing of COVID-19 AE cases will be provided.

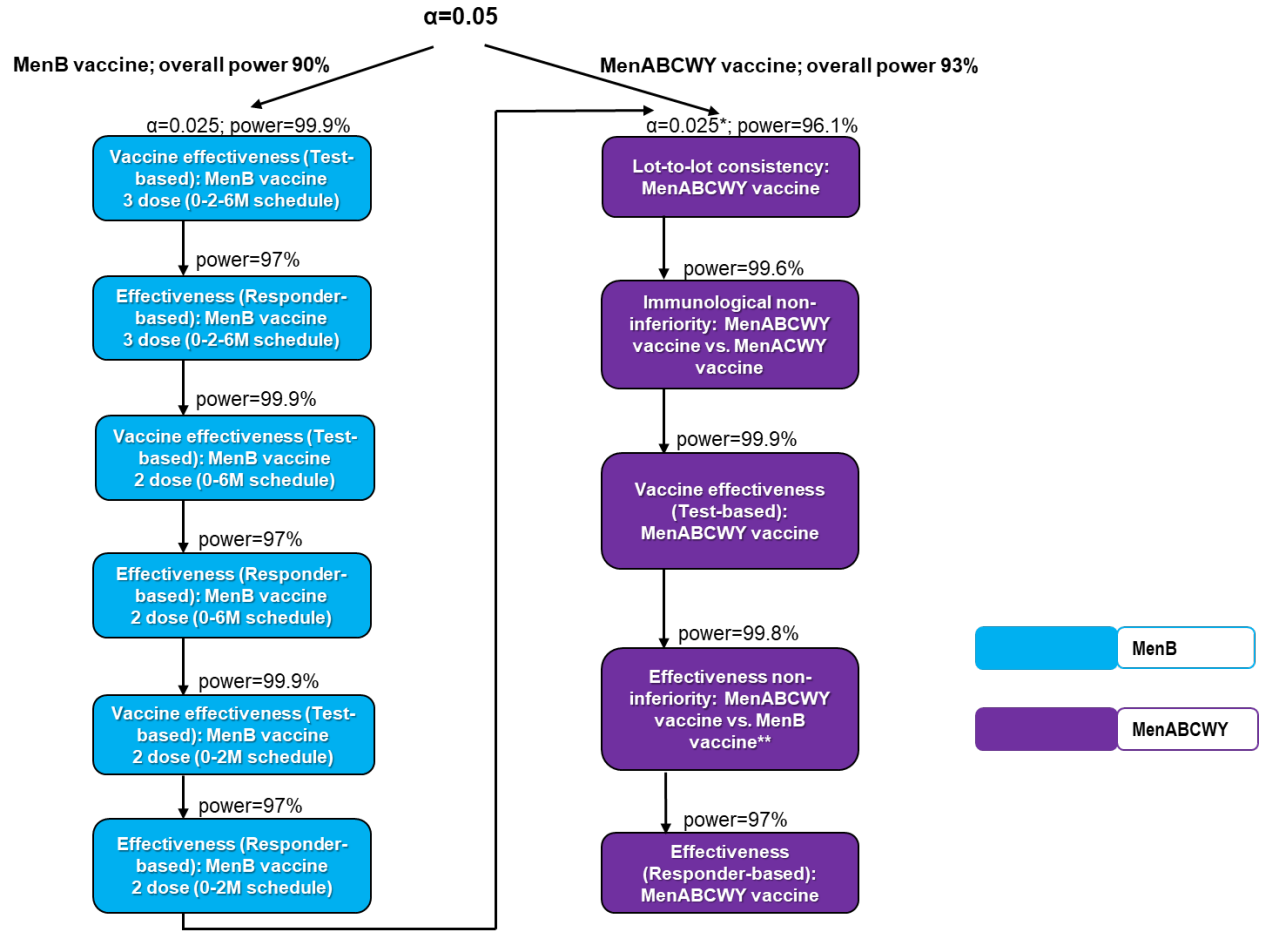
In case for a subject besides ediary data, also solicited reactions were recorded in the CRF, the CRF data will be mapped into the SDTM data with the ediary data (FA domain). For the analysis, the CRF data will be used in case of duplicate data.

6. ANALYSIS INTERPRETATION

Multiple objectives and endpoints require type I error control. Full alpha (0.05) is split equally (alpha=0.025) between rMenB+OMV NZ objectives and MenABCWY objectives. Furthermore, within rMenB+OMV NZ, as well as within MenABCWY, objectives are tested hierarchically. If the first null hypothesis is rejected, then the testing will continue with the second hypothesis at same alpha. Same for 3rd, 4th, and so forth. Whenever a null hypothesis is not rejected, then the testing will stop.

As the comparator for MenABCWY non inferiority objective for the B component will be the selected schedule of rMenB+OMV NZ as determined in this study, the objectives of rMenB+OMV NZ will be analysed first. Additionally, if all null hypotheses related to rMenB+OMV NZ objectives will be rejected, the alpha (alpha=0.025) will be propagated to the MenABCWY part, and hypotheses related to MenABCWY objectives will be tested at full alpha (alpha=0.05). See Figure 2 for an explanation of the hierarchical testing (top to bottom, the order indicated by the arrows).

Figure 2 Hierarchical testing of hypothesis



* Alpha split equally between rMenB+OMV NZ and MenABCWY vaccine objectives.
If all rMenB+OMV NZ objectives achieved, MenABCWY vaccine objectives will be tested at full alpha.
** If all objectives of rMenB+OMV NZ are met, the comparator will be the 0,2-months schedule. If the 0,2-months objective is not met, and the 0,6-months is met, then the 0,6-months schedule will be the comparator. If the 0,6-months is also not met, then the 0,2,6-months schedule will be the comparator.

Refer to Glossary of terms for definitions of test-based and responder-based vaccine effectiveness.

7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

The final study report will contain at least the final analyses of all primary and secondary endpoints.

7.2. Statistical considerations for interim analyses

No interim analysis is planned for this study

8. CHANGES FROM PLANNED ANALYSES

Not applicable

9. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

The following sections describe additional derivation rules and statistical methods which are not presented in section 10.1.

9.1. Data derivation

Not applicable

9.2. Statistical Method

Not applicable

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

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

10.1.1. Attributing events to vaccine doses

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

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

10.1.2. Handling of missing data

10.1.2.1. Dates

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

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

The following exceptions apply:

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

year. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that year.

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

10.1.2.2. Laboratory data

Missing laboratory results (including immunological data) will not be replaced.

10.1.2.3. Daily recording of solicited adverse events

10.1.2.3.1. Studies with electronic diaries

For studies using electronic diaries for the collection of solicited adverse events, a solicited adverse events will be considered present only when a daily recording of grade 1 or more is present.

10.1.2.4. Unsolicited adverse events

Unsolicited adverse event summaries are including serious adverse events unless specified otherwise.

Missing severity, relationship with study vaccine, and outcome of unsolicited adverse events will not be replaced and will appear as 'UNKNOWN' in all statistical output.

10.1.3. Data derivation

10.1.3.1. Age at vaccination in days

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

Age = date of vaccination minus date of birth

10.1.3.2. Age at vaccination in months

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

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

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

10.1.3.3. Age at vaccination in years

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

DOB = 10SEP1983, Date of vaccination = 09SEP2018 -> Age = 34 years

DOB = 10SEP1983, Date of vaccination = 10SEP2018 -> Age = 35 years

10.1.3.4. Weight

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

Weight in kilograms = Weight in pounds / 2.2

10.1.3.5. Height

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

Height in centimeters = Height in inches x 2.54

10.1.3.6. Body mass index (BMI)

BMI will be calculated as follows:

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

10.1.3.7. Temperature

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

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

10.1.3.8. Numerical serology results

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

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

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

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

10.1.3.10. Onset day

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

10.1.3.11. Duration of events

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

10.1.3.12. Counting rules for combining solicited and unsolicited adverse events

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

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

10.1.3.13. Counting rules for occurrences of solicited adverse events

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

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with:

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

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

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

10.1.4.2. Differences in percentages

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

10.1.4.3. Demographic/baseline characteristics statistics

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

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

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

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

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

10.1.4.4. Serological summary statistics

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

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

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

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

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

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

10.1.5.2. Standardized asymptotic confidence intervals around differences in proportions

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

10.2. TFL TOC

The Tables Figures and Listings (TFL) Table of Contents (TOC) which itemizes the planned list of TFL and their associated lay-out is developed as a separate document.

10.3. Glossary of terms

End of Study (EoS) **(Synonym of End of Trial)**	For studies with collection of human biological samples and/or imaging data, the EoS is defined as Last subject last visit (T10). or Last testing results released of samples collected at Visit 6* * In this case EoS must be achieved no later than 8 months after LSLV.
Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.
Responder-based vaccine effectiveness:	The enc-hSBA methodology involves testing the serum samples from each individual subject against a subset of around 35 strains randomly chosen from the overall panel of 110 meningococcus B US strains. Responder-based vaccine effectiveness is assessed based on the percentage of subjects considered responders, i.e., subjects whose serum kills the majority (≥70% in this study) of the tested strains following vaccination.
Test-based vaccine effectiveness:	The enc-hSBA methodology involves testing the serum samples from each individual subject against a subset of around 35 strains randomly chosen from the overall panel of 110 meningococcus B US strains. Test-based vaccine effectiveness is assessed based on the overall percent of individual positive tests following vaccination and represents the reduction in risk compared to the placebo.

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

GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A phase III, randomized, controlled, observer-blind study to demonstrate effectiveness, immunogenicity and safety of GSK's meningococcal Group B and combined ABCWY vaccines when administered to healthy adolescents and young adults.
eTrack study number and Abbreviated Title	205416 [MENB REC 2ND GEN-038 (V72_72)]
Scope:	All data pertaining to the above study
Date of Statistical Analysis Plan	Final: 25 Apr 2022

APP 9000058193 Statistical Analysis Plan Template V4 (Effective date: 3June2019)

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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
Eli Type	Internal database code for type of elimination code
ELISA	Enzyme-linked immunosorbent assay
EOS	End of Study
ES	Exposed Set
FAS	Full Analysis Set
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titre
GSK	GlaxoSmithKline
LL	Lower Limit of the confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
PCD	Primary completion Date
PPS	Per-Protocol Set
RR	Relative Risk
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
TFL	Tables Figures and Listings
TOC	Table of Contents

1. DOCUMENT HISTORY

Date	Description	Protocol Version
25 Jul 2019	First version	Amendment 1: 23 MAY 2019
15 Jun 2020	Amendment 1	Amendment 2: 18 MAR 2020
25 Mar 2022	Amendment 2	Amendment 4: 12 MAY 2021
25 Apr 2022	Amendment 3	Amendment 4: 12 MAY 2021

2. OBJECTIVES/ENDPOINTS

Table 1 Study objectives and endpoints

Objectives	Endpoints
Primary	
Vaccine effectiveness (Test-based): rMenB+OMV NZ To demonstrate the effectiveness of the rMenB+OMV NZ vaccine against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity using enc-hSBA at 1 month after the 3-dose (0,2,6-months) and 2-dose (0,6-months; 0,2-months) vaccination series when compared to 1 month after the MenACWY vaccination. *Criterion* *Lower limit (LL) of the two-sided 97.5% confidence interval (CI) for vaccine effectiveness is above 65% against a randomly selected strain panel between the:* • *MenB_0_2_6 and ACWY groups (for 0,2,6-months schedule)* • *MenB_0_6 and ACWY groups (for 0,6-months schedule),* • *MenB_0_2_6 and ACWY groups (for 0,2-months schedule)*	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at 1 month after the: • 3-dose vaccination series in MenB_0_2_6 group (Day 211, Month 7) • 2-dose vaccination series in MenB_0_6 group (Day 211, Month 7), and • 2-dose vaccination series in MenB_0_2_6 group (Day 91, Month 3) • 1 month after the MenACWY vaccination in ACWY group (Day 31, Month 1).
Effectiveness (Responder-based): rMenB+OMV NZ To demonstrate the effectiveness of the rMenB+OMV NZ vaccine by assessing the percentages of subjects whose sera kill ≥70% of strains tested using enc-hSBA at 1 month after the 3-dose (0,2,6-months) and 2-dose (0,6-months; 0,2-months) vaccination series of the rMenB+OMV NZ. *Criterion:* *LL of the two-sided 97.5% CI for the percentages of subjects whose sera kill ≥70% of strains is above 65%, tested for:* • *MenB_0_2_6 group (for 0,2,6-months schedule)* • *MenB_0_6 group (for 0,6-months schedule),* • *MenB_0_2_6 group (for 0,2-months schedule)*	The percentages of subjects whose sera kill ≥70% of the strains tested using enc-hSBA, at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group), • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group)
The 3 vaccine schedules will be tested for both, test-based and responder-based, in a hierarchical way (starting from 0-2-6, to 0-6 and 0-2). Refer to Protocol Section 10.1 for details on continuing the evaluation.	

Objectives	Endpoints
Lot-to-lot consistency: MenABCWY vaccine To demonstrate lot-to-lot consistency of the immune responses of 3 lots of the MenACWY component of the MenABCWY vaccine, as measured by hSBA GMTs directed against serogroups A, C, W and Y at 1 month after last vaccination (0,6-months). *Criterion:* *The two-sided 97.5% CIs^ for the ratio of hSBA GMTs of antibodies against serogroups A, C, W and Y are within the [0.5;2.0] equivalence interval for each pair of lots.*	GMTs directed against serogroups A, C, W and Y for each lot (ABCWY-1 group, ABCWY-2 group, ABCWY-3 group) at 1 month after the last vaccination (Day 211, Month 7)
Immunological non-inferiority: MenABCWY vaccine vs. MenACWY vaccine To demonstrate the immunological non-inferiority of the MenABCWY vaccine compared to the MenACWY vaccine as measured by the percentages of subjects achieving a 4-fold rise in hSBA titres against *N. meningitidis* serogroups A, C, W and Y at 1 month after the last MenABCWY vaccination (0,6-months) and 1 month after the MenACWY vaccination. *Criterion:* *LL of the 2-sided 97.5% CI^ for the group difference in percentages of subjects achieving a 4-fold rise* in hSBA titres is above -10%.*	The percentages of subjects with 4-fold rise* in hSBA titres against *N. meningitidis* serogroups A, C, W and Y at 1 month after the: • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • 1 month after the MenACWY vaccination for the ACWY group (Day 31, Month 1) relative to baseline (Day 1, Month 0).
Vaccine effectiveness (Test-based): MenABCWY vaccine To demonstrate the effectiveness of the MenABCWY vaccine against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains as measured by enc-hSBA at 1 month after the last MenABCWY vaccination (0,6-months) when compared to 1 month after the MenACWY vaccination. *Criterion:* *LL of the two-sided 97.5% CI^ for vaccine effectiveness is above 65% against a randomly selected strain panel between the ABCWY group (pooled lots) and the ACWY group.*	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at 1 month after the: • last vaccination for the ABCWY group (pooled) (Day 211, Month 7), and • 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1).
Effectiveness non-inferiority: MenABCWY vaccine vs. rMenB+OMV NZ vaccine To demonstrate the non-inferiority of the effectiveness of the MenABCWY vaccine (0,6-months schedule) compared to the rMenB+OMV NZ vaccine (0,2,6-months or 0,6-months or 0,2-months) † in terms of percentage of samples with bactericidal serum activity using enc-hSBA against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains. *Criterion:* *LL of the two-sided 97.5% CI^ for the difference in percentages of samples with bactericidal serum activity using enc-hSBA against a randomly selected panel of*	The percentages of samples with bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains at 1 month after the: • last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • 3-dose vaccination series of rMenB+OMV vaccine (Day 211, Month 7 in MenB_0_2_6 group) or 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) or 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group) †

Objectives	Endpoints
endemic US N. meningitidis serogroup B invasive disease strains is above -5% at 1 month after: • *the last vaccination in ABCWY group (pooled lots) (for 0,6 months schedule), and* • *The last vaccination in MenB_0_2_6 group (for 0,2,6-months schedule) or the last vaccination in MenB_0_6 group (for 0,6-months schedule) or the second vaccination in MenB_0_2_6 group (for 0,2-months schedule*	
Effectiveness (Responder-based): MenABCWY vaccine To demonstrate the effectiveness of MenABCWY vaccine by assessing the percentages of subjects whose sera kill ≥70% of strains tested using enc-hSBA at 1 month after the last vaccination of MenABCWY (0,6-months). *Criterion:* *LL of the two-sided 97.5% CI^ for the percentages of subjects whose sera kill ≥70% of strains tested for MenABCWY is above 65%.*	The percentages of subjects whose sera kill ≥70% of the strains tested using enc-hSBA, at 1 month after the last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7).
Safety To evaluate the safety and reactogenicity of the MenB, MenABCWY, and the MenACWY vaccines	• The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [body temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) adverse events (AEs) during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. • The frequencies and percentages of subjects with any unsolicited AEs (including all SAEs, AEs leading to withdrawal, AESIs and medically attended AEs) during the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. • The percentages of subjects with SAEs, AEs leading to withdrawal, AESIs and medically attended AEs throughout the study period [Month 0 to Month 18].
Secondary	
To demonstrate the immunological non-inferiority of the MenABCWY vaccine compared to the rMenB+OMV NZ vaccine as measured by the percentages of subjects achieving a 4-fold rise in hSBA titres against *N. meningitidis* serogroup B indicator strains at 1 month after the last MenABCWY vaccination (0,6-months schedule) and 1 month after the rMenB+OMV NZ vaccination (0,2,6-months or 0,6-months or 0,2-months) † *Criterion:* *Non-inferiority will be demonstrated if the LL of the 2-sided 95% CI for the group difference in percentage of*	The percentages of subjects with 4-fold rise** in hSBA titres against *N. meningitidis* serogroup B indicator strains at 1 month after the: • last MenABCWY vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • 3-dose vaccination series of rMenB+OMV vaccine(Day 211, Month 7 in MenB_0_2_6 group) or 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) or 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group) † relative to baseline (Day 1, Month 0).

Objectives	Endpoints
*subjects achieving a 4-fold rise** in hSBA titres against N. meningitidis serogroup B indicator strains is above -10%.*	
To assess the effectiveness of the rMenB+OMV NZ and MenABCWY vaccines against each of the randomly selected endemic US *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series when compared to 1 month after the MenACWY vaccination.	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group) • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • MenACWY vaccination (Day 31, Month 1 in ACWY group).
To describe the distribution of subjects by percentages of serogroup B invasive disease strains killed using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series of rMenB+OMV NZ and MenABCWY vaccines.	The percentages of serogroup B invasive disease strains killed using enc-hSBA in each subject at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7)
To assess the immune response to the rMenB+OMV NZ (0,2,6-months, 0,6-months and 0,2-months) and MenABCWY (0,6-months) vaccines against *N. meningitidis* serogroup B indicator strains at pre-vaccination (Day 1, Month 0) and at 1 month after the last MenABCWY vaccination and at 1 month after the second and third vaccination of rMenB+OMV NZ.	The immune response to the rMenB+OMV NZ and ABCWY vaccines will be evaluated by measuring bactericidal activity against *N. meningitidis* serogroup B indicator strains as following: *1. The percentages of subjects with hSBA titres ≥ lower limit of quantitation (LLOQ) for each (individual response) and all (composite response) serogroup B indicator strains at baseline (Day 1, Month 0) and at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *2. The percentages of subjects with 4-fold rise** in hSBA titres at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 90, Month 3 in MenB_0_2_6 group), and

Objectives	Endpoints
	• last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *relative to baseline (Day 1, Month 0).* *3. hSBA GMTs at baseline (Day 1, Month 0) and at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *4. hSBA GMRs at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *relative to the baseline (Day 1, Month 0).*
To assess the immune response to MenABCWY (0,6-months schedule) and MenACWY (single dose) vaccines against *N. meningitidis* serogroups A, C, W and Y, at pre-vaccination (Day 1, Month 0) and at 1 month after the first and the last MenABCWY vaccination and 1 month after the MenACWY vaccination.	*1. The percentage of subjects with hSBA titres ≥ LLOQ for serogroups A, C, W and Y at baseline (Day 1, Month 0) and:* • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1). *2. The percentage of subjects with 4-fold rise* in hSBA titres at 1 month after the:* • first vaccination (Day 31, Month 1) for the ABCWY group (pooled lots) compared to the MenACWY vaccination in the ACWY group (Day 31, Month 1) *relative to baseline (Day 1, Month 0).* *3. hSBA GMTs against N. meningitidis serogroups A, C, W and Y* at baseline (Day 1, Month 0) and: • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1). *4.hSBA GMRs against N. meningitidis serogroups A, C, W and Y at:* • 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots) as compared to baseline (Day 1, Month 0), and

Objectives	Endpoints
	• 1 month after the single MenACWY vaccination in the ACWY group (Day 31, Month 1) as compared to baseline (Day 1, Month 0). *5.The total IgG as measured by ELISA GMCs against serogroups A, C, W and Y* at baseline (Day 1, Month 0) and*:* • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1).

Abbreviations: ELISA = enzyme-linked immunosorbent assay; Enc-hSBA = endogenous complement human serum bactericidal assay; GMC = geometric mean concentrations; GMT = geometric mean titre; GMR = geometric mean ratio; CI = confidence interval; hSBA = human serum bactericidal assay; LOD: limit of detection; LLOQ = lower limit of quantitation; LL = lower limit; AE = Adverse event; SAE = Serious adverse event; AESI = Adverse event of special interest

N.meningitidis serogroup B indicator strains = M14459, 96217, M07-0241084 and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively. The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented either in a protocol amendment or in the clinical report.

Refer to Protocol Section 10 for details on evaluation of objectives and sample size justification. Refer to Glossary of terms for definitions of test-based and responder-based effectiveness

^ If the co-primary effectiveness objectives for rMenB+OMV NZ are met, then all objectives for MenABCWY will be evaluated at 95% CI. Refer to Protocol Section 10.1 for details

† If all objectives of rMenB+OMV NZ are met, the comparator will be the 0,2-months schedule. If the 0,2-months objective is not met, and the 0,6-months is met, then the 0,6-months schedule will be the comparator. If the 0,6-months is also not met, then the 0,2,6-months schedule will be the comparator.

*For the Men A, C, W, Y evaluation, the 4-fold rise is defined as:

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

**For the MenB evaluation, the 4-fold rise per each indicator strain is defined as:

- a post-vaccination‡ hSBA titre ≥4 times the LOD for subjects with a pre-vaccination hSBA titre <LOD
- a post-vaccination‡ hSBA titre ≥4 times the LLOQ for subjects with a pre-vaccination hSBA titre ≥LOD and <LLOQ, and
- a post-vaccination‡ hSBA titre ≥4 times the pre-vaccination hSBA titre for subjects with a pre-vaccination hsBA titre ≥LLOQ

‡ = post-2nd vaccination for 0,6 and 0,2 schedule and post-3rd vaccination for 0,2,6 schedule.

3. STUDY DESIGN

3.1. Scientific rationale for study design

As the rMenB+OMV NZ licensure in the US was issued through accelerated approval, the FDA has requested to demonstrate the effectiveness of the vaccine against an extended panel of serogroup B meningococcal strains (MenB) as a post-marketing commitment in US adolescents and young adults, thus confirming that the vaccine can protect against diverse meningococcal B strains prevalent in the United States.

The availability of a pentavalent meningococcal vaccine in a single administration would however reduce the number of injections and could increase coverage for meningococcal disease caused by *N. meningitidis* serogroups A, B, C, W, and Y worldwide. GSK's investigational MenABCWY combination vaccine is intended to protect against 5 of the most prevalent serogroups of *Neisseria meningitidis* (A, B, C, W, Y) in humans.

Hence, along with the licensed MenB vaccine (*Bexsero*), this Phase III study will also assess the safety, effectiveness, and immunogenicity of the investigational MenABCWY vaccine.

Rationale for effectiveness assessment

As mentioned above, one of the primary purposes of this study is to evaluate the effectiveness of 2 or 3 doses of rMenB+OMV NZ and of 2 doses of the MenABCWY vaccines in healthy adolescents and young adults by measuring the bactericidal activity against 110 endemic US *N. meningitidis* serogroup B strains using an endogenous complement human Serum Bactericidal Assay (enc-hSBA). Sera from the ACWY group receiving the MenACWY vaccine will also be tested against serogroup B meningococcal strains by enc-hSBA as a control for test-based effectiveness assessment. The overall vaccine effectiveness (VE) against all 110 strains combined will be computed by means of a generalised linear model. For additional details see statistical analysis section of the Clinical Study Protocol (Protocol Section 10).

Rationale for lot-to-lot consistency assessment

MenABCWY is a reconstituted vaccine with the lyophilised 'ACWY component' and liquid rMenB+OMV NZ. The MenB component has the same formulation as the commercial *Bexsero*. To demonstrate that the lots of the investigational MenABCWY vaccine are adequately representative of the formulation intended for marketing, equivalence will be assessed for 3 different lots of the ACWY component of the ABCWY vaccine.

Rationale for non-inferiority assessment of MenABCWY vs MenACWY and rMenB+OMV NZ

The study aims to also demonstrate that the investigational combination MenABCWY vaccine is not inferior to a licensed MenACWY vaccine (*Menveo*) and a licensed MenB vaccine (*Bexsero*) which are part of the current standards of care in the US for prevention of invasive disease caused by *N. meningitidis* serogroups A, C, W, Y and by *N. meningitidis* serogroup B, respectively.

Rationale for blood volume collected:

In order to provide the necessary serum volume for the bactericidal assays (enc-hSBA and/ or hSBA(s)), 25 mL whole blood will be collected at Visit 2, Visit 4 and Visit 6. At pre-vaccination (Visit 1), 20 mL whole blood will be collected to provide the necessary serum volume for the hSBA.

Blood samples are taken from all subjects irrespective of the testing status in order to maintain the study blind. Refer to Protocol Section 8.4.2.1 for further details.

Rationale for the selected vaccination schedules

rMenB+OMV NZ: This study aims at demonstrating the VE of the rMenB+OMV NZ vaccine administered as 2-dose vaccine, either with a shorter interval (0,2-months) or a prolonged interval (0,6-months) between doses. A 3-dose schedule has been also added to better characterise the VE.

Note: The rMenB+OMV NZ in the ACWY group is administered in a 0,1-months schedule. This interval is within the recommendations in the summary of product characteristics of *Bexsero* and helps in maintaining the blind. No objectives are associated with this schedule of rMenB+OMV NZ.

MenABCWY: A number of different vaccine formulations were evaluated in MenABCWY Phase I and II clinical studies. The formulation with the same active ingredient composition as the rMenB+OMV NZ (*Bexsero*) and MenACWY (*Menveo*) vaccines was chosen as the final formulation of the investigational MenABCWY vaccine. Two doses administered 6 months apart (0,6-months) is considered the optimal dosing schedule, based on serogroup B immunogenicity results from MenABCWY Phase II clinical studies.

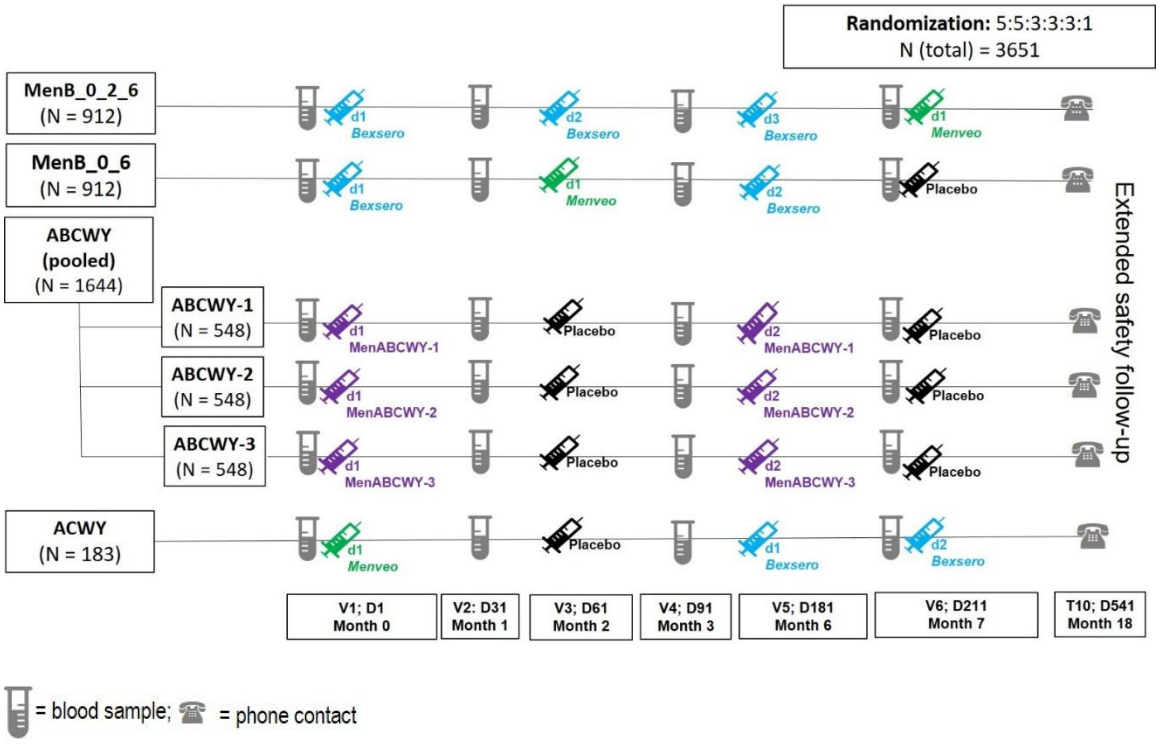
MenACWY: As a comparator for serogroup A, C, W, and Y vaccine effectiveness and immune responses, a single dose of MenACWY vaccine is administered to subjects in the ACWY group. To conform with the standard of care (also in alignment with current ACIP routine immunisation recommendations in US), subjects in the MenB_0_2_6 and MenB_0_6 groups will also receive a dose of MenACWY at Day 211 and Day 61, respectively.

3.1.1. Rationale for the use of placebo

For this study, a placebo (saline solution) will be administered as presented in Figure 1. A placebo is the only available option to minimize possible introduction of reporting bias in collecting information about AEs and to ensure the same number of vaccinations are administered to subjects assigned to either of the six study groups.

3.2. Overall design

Figure 1 Study design overview



N = number of subjects; d = dose; V = visit; D = day; T=Telephone call
Refer to Protocol Table 3 for details on all visits
Note: Home visits may be performed only by sites authorised (as per local regulations and sponsor agreement), with approved site level standard operating procedures (SOP) provided that the compliance with protocol procedures are ensured.

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the schedule of activities (Protocol Section 2), are essential and required for study conduct.

- Type of study: self-contained

- Experimental design: This is a phase III, randomised, controlled, observer-blind, multi-center study to evaluate effectiveness, immunogenicity and safety of rMenB+OMV NZ and MenABCWY vaccines. A total of 3651 healthy adolescents and young adults aged 10-25 years will be enrolled and randomised (5:5:3:3:3:1 ratio) to one of the six parallel study groups:

  – **MenB_0_2_6 group***: subjects will receive 3 doses of rMenB+OMV NZ at Day 1, Day 61 and Day 181 (0, 2 and 0,2,6-months schedule). These subjects will receive 1 dose of the MenACWY vaccine at Day 211**.

  – **MenB_0_6 group**: subjects will receive 2 doses of rMenB+OMV NZ at Day 1 and Day 181 and 1 dose of MenACWY vaccine at Day 61 (rMenB+OMV NZ, 0,6-months schedule). These subjects will receive 1 dose of placebo at Day 211**.

  – **ABCWY-1**: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 1 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211**.

  – **ABCWY-2**: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 2 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211**.

  – **ABCWY-3**: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 3 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211**.

  – **ACWY group**: subjects will receive 1 dose of MenACWY vaccine at Day 1, 1 dose of placebo at Day 61 and 2 doses of rMenB+OMV NZ at Day 181 and Day 211**.

  * MenB_0_2_6 group will also be evaluated for objectives pertaining to 0,2-months vaccination schedule.

  Note 1: A MenB lot will be used for the pre-filled syringe component of the MenABCWY vaccine.

  Note 2: The groups ABCWY-1, ABCWY-2, ABCWY-3 will be pooled into a single group, ABCWY (pooled lots) (except for analysis of lot to lot consistency).

  ** Note 3: In order to let the subjects in MenB_0_2_6 group receive a dose of MenACWY vaccine and for subjects in ACWY group to receive the second dose of rMenB+OMV NZ in line with the vaccine as standard of care (also in line with the Advisory Committee on Immunization Practices (ACIP) recommendations in the US [ACIP, 2011]), the subjects in these groups will receive a vaccination of MenACWY and rMenB+OMV NZ vaccines, respectively, on Day 211 (Visit 6) after completion of the post-vaccination 3 blood sampling. To maintain the blinding of the study, subjects in the rest of the groups (MenB_0_6, ABCWY-1, ABCWY-2 and ABCWY-3) will receive a dose of Placebo. All these vaccines/ product administered at Day 211 are not associated with any study objectives/ endpoints (Safety assessment

conducted after 1 dose of rMenB+OMV NZ in the ACWY group at Day 181 is to maintain the blind of the study).

- Duration of the study: The study duration is approximately 18 months for each subject.
- Primary completion Date (PCD): T10; Day 541.

Refer to Glossary of terms for the definition of PCD.

- End of Study (EoS): the date of release of the last testing results, to be achieved not later than 8 months after Last Subject Last Visit (LSLV) (LSLV = T10; Day 541). If the completion of testing occurs prior the completion of the LSLV the latter date defines the end of study visit.

Refer to Glossary of terms for the definition of EoS.

- Study groups:

Table 2 Study groups and treatment foreseen in the study

Study Groups	Number of subjects	Age (Min-Max)	Treatment name	Vaccine/Product name
MenB_0_2_6	912	10 – 25 y	*Bexsero* (Injection)	rMenB+OMV NZ
			Menveo (Injection)	MenACWY
MenB_0_6	912		*Bexsero* (Injection)	rMenB+OMV NZ
			Menveo (Injection)	MenACWY
			Placebo (Injection)	NaCl
ABCWY-1	548		MenABCWY (with Lot 1 of ACWY) (Injection)	MenABCWY-1
			Placebo (Injection)	NaCl
ABCWY-2	548		MenABCWY (with Lot 2 of ACWY) (Injection)	MenABCWY-2
			Placebo (Injection)	NaCl
ABCWY-3	548		MenABCWY (with Lot 3 of ACWY) (Injection)	MenABCWY-3
			Placebo (Injection)	NaCl
ACWY	183		*Menveo* (Injection)	MenACWY
			Placebo (Injection)	NaCl
			Bexsero (Injection)	rMenB+OMV NZ

Table 3 Overview of study design: Vaccination and Blood Draw Schedule

Visits **Study Day**	**Visit 1** **Day 1**	Visit 2 Day 31	**Visit** 3 **Day 61**	**Visit** 4 **Day 91**	**Visit** 5 **Day 181**	**Visit** 6 **Day 211**
Group **MenB_0_2_6** **N=912**	Pre-vacc Blood sample rMenB+OMV NZ	Post-vacc 1 Blood sample	rMenB+OMV NZ	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample MenACWY
Group **MenB_0_6** **N=912**	Pre-vacc Blood sample rMenB+OMV NZ	Post-vacc 1 Blood sample	MenACWY	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample Placebo
Group **ABCWY-1** **N=548**	Pre-vacc Blood sample MenABCWY-1	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-1	Post-vacc 3 Blood sample Placebo
Group **ABCWY-2** **N=548**	Pre-vacc Blood sample MenABCWY-2	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-2	Post-vacc 3 Blood sample Placebo
Group **ABCWY-3** **N=548**	Pre-vacc Blood sample MenABCWY-3	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-3	Post-vacc 3 Blood sample Placebo
Group **ACWY** **N=150**	Pre-vacc Blood sample MenACWY	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample rMenB+OMV NZ

N = number of subjects; Pre-vacc = pre-vaccination; Post-vacc = post-vaccination

- Treatment allocation: At Day 1, prior to the study vaccination, subjects will be randomised to 1 of the 6 study groups according to a 5:5:3:3:3:1 ratio.
- Blinding: Observer-blind. Kindly refer to Protocol Section 7.3 for details on blinding and unblinding procedures.
- Sampling schedule:
  - A total of 4 blood samples* will be collected from each subject at Day 1 (pre-vaccination blood sample; approximately 20 mL), at Day 31 (post-vaccination 1 blood sample; approximately 25 mL), at Day 91 (post-vaccination 2 blood sample; approximately 25 mL) and at Day 211 (post-vaccination-3 blood sample; approximately 25 mL).
  - Urine sampling: Urine samples for pregnancy testing will be collected from female subjects of child-bearing potential at Visit 1 (Day 1), Visit 3 (Day 61), Visit 5 (Day 181) and Visit 6 (Day 211) prior to the vaccination.

  * Insufficient blood volume may lead to test cancellation and jeopardise the statistical power. Hence, every effort must be done to collect blood volume as per protocol requirements.
- Data collection: standardised Electronic Case Report Form (eCRF). Solicited symptoms will be collected using a subject Diary (electronic Diary [eDiary]).
- Safety monitoring: Regular safety follow-up will be done through telephone calls (T). There will also be an extended safety follow-up (ESFU) phone call 12 months post-vaccination 3 (Day 181; Visit 5). This ESFU phone call will also mark the study conclusion. Refer to Protocol Table 3 and Protocol Section 8.5.3 for details on the safety follow-up.

3.3. Number of subjects

A total of 3651 subjects will be randomised in a ratio of 5:5:3:3:3:1; 912 each in MenB_0_2_6 and MenB_0_6 groups, 548 in each ABCWY groups and 183 in ACWY group. Assuming a 25% drop out rate, this should provide approximately 684 evaluable subjects in each of the MenB groups, 411 evaluable subjects in each of the ABCWY groups and 137 evaluable subjects in the ACWY group.

Refer to Protocol Section 10.1 for a detailed description of the criteria used in the determination of sample size.

Withdrawals will not be replaced.

3.4. Subject and study completion

A subject is considered to have completed the study, if the subject is available for the concluding contact (T10; Day 541) as described in the protocol.

Global completion of the study is required in order to provide enough subjects as defined in Protocol Section 10.1 Sample Size Determination.

4. ANALYSIS SETS

4.1. Definition

For purposes of analysis, the following analysis sets are defined:

4.1.1. Enrolled Set

Subject/ Subject for whom parent(s)/LAR's agreed to participate in a clinical study after completion of the informed consent process, who meet screening/eligibility criteria and randomized and/or received study intervention or undergone an invasive procedure.

4.1.2. Exposed Set

All subjects who received at least 1 dose of the study treatment. The allocation in a group is done in function of all administered treatments.

4.1.3. Full Analysis Set

All subjects who received at least 1 dose of the study treatment and have post-vaccination effectiveness or immunogenicity data.

4.1.4. Per Protocol Set

All subjects in the Full Analysis Set minus subjects with protocol deviations that lead to exclusion from the Per Protocol Set.

4.1.5. Solicited Safety Set

All subjects who received at least 1 dose of the study treatment (Exposed Set) who have solicited safety data beyond 30 minutes post vaccination.

4.1.6. Unsolicited Safety Set

All subjects who received at least 1 dose of the study treatment (Exposed Set) that report unsolicited AEs/report not having unsolicited AEs.

4.1.7. Overall Safety Set

All subjects that belong to the Unsolicited safety or/and to the Solicited safety set.

4.2. Criteria for eliminating data from Analysis Sets

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

4.2.1. Elimination from Exposed Set (ES)

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

4.2.2. Elimination from Per protocol Set (PPS)

4.2.2.1. Excluded subjects

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

Table 4 Elimination code and condition to exclude a subject from the PPS analysis

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
800	Fraudulent data	All	All
900	Invalid informed consent	All	All
1030	Study vaccine not administered at all	All	All
1050	Randomization failure	Visit 1, 3, 5	All
1060	Randomization code was broken	All	All
1070.1	Subjects got vaccinated with the correct vaccine but containing a lower volume	Visit 1, 3, 5	All
1070.2	Vaccination not according to protocol	Visit 1, 3, 5	All
1080	Vaccine temperature deviation	Visit 1, 3, 5	All
1090	Expired vaccine administered	Visit 1, 3, 5	All
1500.1	Other deviation from study procedures not able to classified under any other categories	All	All
1500.2	Any other GCP non-compliance not able to classified under any other categories	All	All
2010	Protocol violation (inclusion/exclusion criteria)	All	All
2040	Administration of any medication forbidden by the protocol	Visit 1, 3, 5	All
2050	Not withdrawn after developing withdrawal criteria other than prohibited concomitant vaccination/medication (medical condition forbidden)	All	All
2060	Concomitant infection related to the vaccine which may influence immune response (only meningococcal infection)	All	All
2080	Subjects did not comply with vaccination schedule	Visit 3, 5	All

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
2090	Subjects did not comply with blood sample schedule	Visit 2, 4, 6	All
2100	Serological results not available post-vaccination for all tests	Visit 2, 4, 6	All
2120	Obvious incoherence or abnormality or error in data related to testing	Visit 2, 4, 6	All
2130	Biological sample specimen procedures not compliant with protocol	Visit 2, 4, 6	All

4.2.3. Elimination from unsolicited and solicited safety set

4.2.3.1. Excluded subjects

4.2.3.1.1. Unsolicited safety set

Code 1030 (Study vaccine not administered at all), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1150 (no post-vaccination safety data) will be used for identifying subjects eliminated from the unsolicited safety set.

4.2.3.1.2. Solicited safety set

Code 1030 (Study vaccine not administered at all), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1160 (no post-vaccination solicited safety data) will be used for identifying subjects eliminated from the solicited safety set.

5. STATISTICAL ANALYSES

Standard data derivation rules and statistical methods are described in section 10.1 while the study specific data derivation rules and stat methods are described in section 9.

5.1. Disposition of subjects

5.1.1. Analysis of disposition of subjects planned in the protocol

Number of subjects enrolled, vaccinated subjects (at least 1 vaccination, full vaccination course), reason for early withdrawal, FAS, and PPS will be described by vaccine group.

5.1.2. Additional considerations

Not applicable

5.2. Demography and baseline characteristics analyses

5.2.1. Analysis of demography and baseline characteristics planned in the protocol

Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age, height, weight, and body mass index (BMI) at enrolment will be calculated overall and by vaccine group.

Distributions of subjects by sex, race, ethnic origin will be summarised overall and by vaccine group.

5.2.2. Additional considerations

A summary table of important protocol deviations related to COVID-19 will be provided. Also, a listing will be produced.

5.3. Primary effectiveness and immunogenicity

5.3.1. Analysis of primary effectiveness and immunogenicity planned in the protocol

Refer to Glossary of terms for definitions of test-based and responder-based vaccine effectiveness. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then all objectives for MenABCWY will be evaluated at 95% CI (Sections 5.3.1.7 through 5.3.1.11, ref Protocol Section 10.1).

5.3.1.1. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Analysis set: Per-protocol set (PPS) will be the primary analysis population

Statistical method: The VE is defined as 1- RR= (1- percentage of samples without bactericidal serum activity at 1:4 dilution in MenB group / percentage of samples without bactericidal serum activity at 1:4 dilution in the ACWY group) x100% and it will be analyzed using a generalised linear model with vaccine group, strain, and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) as independent variables. Furthermore, a repeated statement will be used to estimate the variance of the RR including correlation within subject's responses to different strains. If the statistical model does not converge due to (one of) the factor(s), a model without this/these factor(s) will be fitted instead. The response variable of the model will be the Bernoulli distributed outcome without bactericidal activity at a 1:4 dilution (i.e. response is 1 if titre < 4, and 0 if titre ≥ 4), at 1 month after the last vaccination (Month 7) in the MenB group and at Month 1 for the ACWY group. Each subject will contribute with approximately 35 measures to this analysis, each of the measures corresponding to the response variable to one of the 35 strains randomly assigned to be tested with the samples available for that specific subject.

In order to obtain the VE measure which is a measure based on the relative risk (RR), a generalised linear model will be used with the Binary distribution and link function log in order to compute the log RR and the corresponding 97.5% CI. The obtained values will be exponentiated to obtain the RR and the corresponding 97.5% CI. The VE will be computed as 100% x (1 – RR). Effectiveness of rMenB+OMV NZ (0,2,6-months schedule) will be demonstrated if the lower limit of the two-sided 97.5% CI for VE between MenB and the ACWY group is above 65%.

5.3.1.2. Effectiveness (Responder-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Analysis set: FAS will be the primary analysis population.

Statistical method: The percentage of responders (see definition in Glossary of terms) and the corresponding exact two-sided 97.5% CI based on Clopper-Pearson method will be calculated [Clopper, 1934].

The objective is to demonstrate that the lower limit of the 97.5% CI for the percentage of responders is higher than 65%.

5.3.1.3. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 5.3.1.1

5.3.1.4. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 5.3.1.2

5.3.1.5. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 5.3.1.1

5.3.1.6. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 5.3.1.2

5.3.1.7. Lot-to-lot consistency: MenABCWY - ACWY component

Analysis set: The analysis of lot-to-lot consistency will be based on the PPS.

Statistical method: For each of the three ABCWY lots (Lots 1, 2 and 3 of the MenACWY component of the ABCWY vaccine), GMTs and 97.5% CIs will be calculated by exponentiating (base 10) the least squares means and the lower and upper limits of the 97.5% CIs of the log transformed titres (base10) obtained from an Analysis of Variance

(ANOVA) with factors for vaccine lot and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)). Additionally, lot-to-lot GMT ratios will be computed for each pair of ABCWY lots. Ninety-seven point five percent (97.5%) CIs for the ratios of GMTs will be constructed by exponentiating the difference of the least square means of the log transformed titres and the lower and upper limits of the 97.5% CIs on the difference obtained from the ANOVA model above.

Lot-to-lot consistency criterion: The three ABCWY lots will be considered equivalent if for each of the 4 serogroups A, C, W and Y and each pair of vaccine lots, the two-sided 97.5% CI on the ratio of GMTs at 1 month after the last vaccination will be contained within the interval [0.5, 2.0].

If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.1.8. Immunological non-inferiority: MenABCWY vs. MenACWY

Analysis set: PPS restricted to subjects without previous ACWY vaccination will be the primary analysis population.

Statistical method: The percentage of subjects with 4-fold rise* in hSBA titres against MenACWY indicator strains A, C, W and Y and the corresponding exact two-sided 97.5% CIs based on Clopper-Pearson method will be calculated for the ABCWY (pooled lots) group and the ACWY group [Clopper, 1934]. The 97.5% CIs for the difference in percentages between ABCWY (pooled lots) and ACWY group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-Inferiority criterion: Non-inferiority of MenABCWY vaccine for the proportion of subjects with 4-fold rise will be demonstrated if the lower limit of the two-sided 97.5% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY (pooled) lots –ACWY) is above -10%.

* For the Men A, C, W, Y evaluation, the 4-fold rise is defined as:

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

Table 5 reads the LOD and LLOQ of MenACWY indicator strains used in the definition of 4-fold rise provided by the laboratory.

Table 5 LOD and LLOQ of MenACWY indicator strains

Strain	LOD	LLOQ
Men A (3125)	CCI [redacted]	
Men C (C11)		
Men W (240070)		
Men Y (860800)		

If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.1.9. Vaccine effectiveness (Test-based): MenABCWY

See Section 5.3.1.1. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the VE for MenABCWY will be evaluated at 95% CI.

5.3.1.10. Effectiveness non-inferiority: MenABCWY vs. rMenB+OMV NZ

Analysis set: PPS will be the primary analysis population.

Statistical method: The percentage of samples with bactericidal activity measured by enc-hSBA at 1:4 dilution and the corresponding exact two-sided 97.5% CIs based on Clopper-Pearson method will be calculated for the ABCWY (pooled lots) group and the MenB group comparator that will be selected (ref: the footnote of Figure 2). The 97.5% CIs for the difference in percentages between ABCWY (pooled lots) and selected MenB group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-Inferiority criterion: Non-inferiority of MenABCWY vaccine for the percentage of samples with bactericidal activity measured by enc-hSBA at 1:4 dilution will be demonstrated if the lower limit of the two-sided 97.5% CI for the difference between the 2 groups (ABCWY (pooled) lots – MenB) is above -5%.

If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.1.11. Effectiveness (Responder-based): MenABCWY

See Section 5.3.1.2. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the effectiveness (responder-based) for MenABCWY will be evaluated at 95% CI.

5.3.2. Additional considerations

Analyses of the primary effectiveness and immunogenicity objectives will be repeated by age group (10-17 years of age and 18-25 years of age), race, sex, region (US/ ex-US), and subjects with and without a previous MenACWY vaccination (primed and unprimed).

5.3.2.1. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

The SAS code to analyse the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) objective is specified below. Treatment, region, age category, previous ACWY vaccination, and strains will be modelled as fixed effect. To account for a possible over-dispersion, the DSCALE option in the model statement will be evaluated first. The DSCALE will be kept in the model only if the F-statistics for the DSCALE parameter is significant ($p<0.05$). The following SAS code will be used for the VE calculation:

```
ods trace on;
ods output GEEEmpPEst = genmod_stats
CONVERGENCESTATUS = converge ;

PROC GENMOD data=dataset descending;
class trtgrp strain region agecat previousACWY subject_id ;
model outcome = trtgrp strain region agecat previousACWY / dist= bin
link= log DSCALE;
repeated subject = subject_id / type= CS withinsubject= strain;
estimate 'MenB026-ACWY' trtgrp 1 0 0 0 0 -1/ alpha=0.025 exp;

/*trtgrp R is MenB0,2,6 and trtgrp W is ACWY*/

run;

ods output close;

data genmod_stats;
set genmod_stats;
where parm = 'trtgrp' and level1 = '1';
rr = exp(estimate);
ub = exp(uppercl);
ve = (1 - rr)*100 ;
ve_ll = (1 - ub) * 100 ;
if ve_ll > 65 then success = 1 ;
else success = 0 ;
run;
```

where outcome represents the Bernoulli distributed outcome without bactericidal activity at a 1:4 dilution (i.e. response is 1 if titre < 4, and 0 if titre ≥ 4), one month after the 3rd vaccination in MenB 0,2,6 and one month after the MenACWY vaccination for the ACWY arm, trtgrp indicates the vaccine groups, strain is the serogroup B strain variable, region is either US or ex-US, agecat is the age at enrolment (10-17 YoA or 18-25 YoA), and previousACWY is previous ACWY vaccination (y/n) at enrolment.

rr is the relative risk (RR), which is obtained from the estimated parameters from PROC GENMOD. Vaccine effectiveness (VE) is then derived as (1-rr)x100%.

ub represents the upper bound of the 97.5% CI of the relative risk. ve_ll is the lower bound of the 97.5% CI for VE, if the value is greater than 65%, then the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) objective is successful.

5.3.2.2. Effectiveness (Responder-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Not applicable

5.3.2.3. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 5.3.2.1, with the difference in the treatment arm:

```
PROC GENMOD data=dataset descending;
class trtgrp strain region agecat previousACWY subject_id ;
model outcome = trtgrp strain region agecat previousACWY / dist= bin
link= log DSCALE ;
repeated subject = subject_id / type= CS withinsubject= strain ;
estimate 'MenB06-ACWY' trtgrp 0 1 0 0 0 -1/ alpha=0.025 exp;

/*trtgrp S is MenB0,6 and trtgrp W is ACWY*/

run;
```

5.3.2.4. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

Not applicable

5.3.2.5. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 5.3.2.1, with the difference the outcome data for group R is from one month after the 2nd vaccination instead of one month after the 3rd vaccination.

5.3.2.6. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

Not applicable

5.3.2.7. Lot-to-lot consistency: MenABCWY - ACWY component

Not applicable

5.3.2.8. Immunological non-inferiority: MenABCWY vs. MenACWY

As a sensitivity analysis, a parametric model will be run. A generalized linear model with factors for vaccine group and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA)) will be ran, with the Binary distribution and link function is identity, and outcome is 4-fold rise. If the lower limit of the two-sided 97.5% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY (pooled) lots –ACWY) coming from the model is above -10%, also the sensitivity analysis has demonstrated non-inferiority. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.2.9. Vaccine effectiveness (Test-based): MenABCWY

See Section 5.3.2.1, with the difference in the estimate statement:

```
PROC GENMOD data=dataset descending;
class trtgrp strain region agecat previousACWY subject_id ;
model outcome = trtgrp strain region agecat previousACWY / dist= bin
link= log DSCALE ;
repeated subject = subject_id / type= CS withinsubject= strain ;
estimate 'MenABCWY-ACWY' trtgrp 0 0 1 1 1 -3/ alpha=0.025 exp
divisor=3;

/*trtgrp T, U, and V are the ABCWY-1, ABCWY-2, and ABCWY-3 lots and
trtgrp W is ACWY*/
run;
```

5.3.2.10. Effectiveness non-inferiority: MenABCWY vs. rMenB+OMV NZ

As a sensitivity analysis, a parametric model will be run. A generalized linear model with factors for vaccine group and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) will be ran, with the Binary distribution and link function is identity, and outcome is bactericidal activity measured by enc-hSBA at 1:4 dilution. If the lower limit of the two-sided 97.5% CI for the difference in percentage of samples with bactericidal activity measured by enc-hSBA at 1:4 dilution between the 2 groups (ABCWY (pooled) lots –MenB) coming from the model is above -5%, also the sensitivity analysis has demonstrated non-inferiority. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

In addition to the comparison of MenABCWY vs the selected MenB schedule per Section 5.3.1.10, MenABCWY will be compared to the other MenB schedule/schedules, whichever is applicable in the same way as described in Section 5.3.1.10. If MenB 0,2 schedule is selected as comparator, in addition MenABCWY will be compared to Menb 0,6 and MenB 0,2,6 schedule. If MenB 0,6 schedule is selected as comparator, in addition MenABCWY will be compared to MenB 0,2,6 schedule. No success criterion is defined for these group comparisons.

5.3.2.11. Effectiveness (Responder-based): MenABCWY

Not applicable

5.4. Secondary effectiveness and immunogenicity

5.4.1. Analysis of secondary effectiveness and immunogenicity planned in the protocol

5.4.1.1. Immunological non-inferiority: MenABCWY vs. rMenB+OMV NZ

Analysis set: PPS will be the primary analysis population.

Statistical method: The percentages of subjects with 4-fold rise** in hSBA titres against N. meningitidis serogroup B indicator strains (M14459, 96217, M07-0241084* and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively) at 1 month after the last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) and 1 month after the 3-dose vaccination series (Day 211, Month 7) in MenB_0_2_6 group or 2-dose vaccination series (Day 211, Month 7) in MenB_0_6 group or 2-dose vaccination series (Day 91, Month 3) in MenB_0_2_6 group and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated [Clopper, 1934]. The 95% CIs for the difference in percentages between ABCWY group (pooled lots) and MenB_0_2_6 group and MenB_0_6 group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-inferiority criterion: Non-inferiority of MenABCWY vaccine for the proportion of subjects with 4-fold rise will be demonstrated if the lower limit of the 2-sided 95% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY group (pooled lots) –selected MenB group) is above -10%.

* The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented either in a protocol amendment or in the clinical report.

** For the MenB evaluation, the 4-fold rise per each indicator strain is defined as:

- a post-vaccination‡ hSBA titre ≥4 times the LOD for subjects with a pre-vaccination hSBA titre <LOD
- a post-vaccination‡ hSBA titre ≥4 times the LLOQ for subjects with a pre-vaccination hSBA titre ≥LOD and <LLOQ, and
- a post-vaccination‡ hSBA titre ≥4 times the pre-vaccination hSBA titre for subjects with a pre-vaccination hSBA titre ≥LLOQ

‡ = post-2nd vaccination for 0,6 and 0,2 schedule and post-3rd vaccination for 0,2,6 schedule).

Table 6 reads the LOD and LLOQ of hSBA titres against N. meningitidis serogroup B indicator strains used in the definition of 4-fold rise provided by the laboratory.

Table 6 LOD and LLOQ of hSBA titres against N. meningitidis serogroup B indicator strains

Strain	LOD	LLOQ
NZ98-254	CCI [redacted]	
96217		
M14459		
M13520		

5.4.1.2. Effectiveness by each of the endemic US N. meningitidis serogroup B strains

Analysis set: FAS will be the primary analysis population. The ABCWY (pooled lots) group and the MenB group comparator that will be selected (ref: the footnote of Figure 2) will be used for the purpose of this analysis.

Statistical method: The VE per strain will be calculated as described in Section 5.3.1.1, using a generalised linear model with vaccine group, and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) as independent variables, and alpha=0.05 leading to 95% CI. In case for a strain 100% response will be observed in both vaccine groups, VE against these strain will be assessed by calculating 95% CI for relative risk from raw proportions, and VE=1-RR.

5.4.1.3. Distribution of percentages of serogroup B invasive disease strains killed

Analysis set: FAS will be the primary analysis population. The ABCWY (pooled lots) group and the MenB group comparator that will be selected (ref: the footnote of Figure 2) will be used for the purpose of this analysis.

Statistical method: Summary statistics of the percentage of serogroup B invasive disease strains killed within a subject using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series of rMenB+OMV NZ and MenABCWY vaccines.

Summary statistics and 95% CI for the mean percentage will be presented, as well as a Figure of the cumulative distribution function.

5.4.1.4. Immune response of MenABCWY, rMenB+OMV NZ and MenACWY

Analysis set: The analysis will be based on the FAS.

Statistical method: The hSBA titres at each time point for all groups (ABCWY group (pooled lots), MenB_0_2_6 and MenB_0_6 groups) will be logarithmically transformed (base10) to fulfil the normal distribution assumption. For each N. meningitidis serogroup A, C, W and Y and each B indicator strain (M14459, 96217, M07-0241084* and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively), the GMTs and GMRs (post-vaccination/baseline) will be obtained from an Analysis of Variance (ANOVA) with factors for vaccine group, region (US/ex-US), age category (10-17 YoA/18-25 YoA), and previous MenACWY vaccination (y/n), and then exponentiating the log-transformed means and their 95% CIs. The ratio of GMTs and GMRs between two groups and the corresponding CI will be estimated additionally.

The total IgG (as measured by ECL) against serogroups A, C, W and Y at baseline (Day 1, Month 0) and

- at 1 month after the first (Day 31, Month 1) and the last vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and
- at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1),

will be analyzed in a comparable way as described above for hSBA titres. Since total IgG is measured as concentration instead of titer, the resulting geometric mean of the concentrations is abbreviated as GMC.

For each N. meningitidis A, C, W and Y and for each (individual response) and all (composite response serogroup B indicator strain (M14459, M07-0241084*, 96217and NZ98/254) the percentages of subjects with hSBA titres ≥LLOQ and of subjects with 4-fold rise and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated for each study group at each timepoint not previously analyzed. Ninety-five percent (95%) CIs for the difference in percentages between ABCWY (pooled lots) on the one hand and MenB_0_2_6, MenB_0_6, and ACWY groups, respectively, on the other hand, will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

* The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented either in a protocol amendment or in the clinical report.

5.4.2. Additional considerations

5.4.2.1. Immunological non-inferiority: MenABCWY vs. rMenB+OMV NZ

As a sensitivity analysis, a parametric model will be run. A generalized linear model with factors for vaccine group and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) will be ran, with the

Binary distribution and link function is identity, and outcome is 4-fold rise. If the lower limit of the two-sided 95% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY (pooled) lots –MenB) coming from the model is above -10%, also the sensitivity analysis has demonstrated non-inferiority.

5.4.2.2. Effectiveness by each of the endemic US N. meningitidis serogroup B strains

The SAS code to analyse the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) by strain is specified below. Treatment, and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) will be modelled as fixed effect. To account for a possible over-dispersion, the DSCALE option in the model statement will be evaluated first. The DSCALE will be kept in the model only if the F-statistics for the DSCALE parameter is significant ($p<0.05$). The following SAS code will be used for the VE calculation:

```
ods trace on;
ods output  GEEEmpPEst = genmod_stats
CONVERGENCESTATUS = converge ;

PROC GENMOD data=dataset descending;
class trtgrp region agecat previousACWY;
by strain ;
model outcome = trtgrp region agecat previousACWY / dist= bin link= log
DSCALE alpha=0.05;
estimate 'MenB026-ACWY' trtgrp 1 0 0 0 0 -1/ alpha= 0.05 exp;

/*trtgrp R is MenB0,2,6 and trtgrp W is ACWY*/

run;

ods output close;

data genmod_stats;
set genmod_stats;
by strain ;
where parm = 'trtgrp' and level1 = '1';
rr = exp(estimate);
ub = exp(uppercl);
ve = (1 - rr)*100 ;
ve_ll = (1 - ub) * 100 ;
if ve_ll > 65 then success = 1 ;
else success = 0 ;
run;
```

where outcome represents the Bernoulli distributed outcome without bactericidal activity at a 1:4 dilution (i.e. response is 1 if titre < 4, and 0 if titre ≥ 4), one month after the 3rd vaccination in MenB0,2,6 and one month after the MenACWY vaccination for the ACWY arm, trtgrp indicates the vaccine groups, strain is the serogroup B strain variable, region is either US or ex-US, agecat is the age at enrolment (10-17 YoA or 18-25 YoA), and previousACWY is previous ACWY vaccination (y/n) at enrolment.

rr is the relative risk (RR), which is obtained from the estimated parameters from PROC GENMOD. Vaccine effectiveness (VE) is then derived as (1-rr)x100%.

ub represents the upper bound of the 95% CI of the relative risk. ve_ll is the lower bound of the 95% CI for VE, if the value is greater than 65%, then the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) objective is successful.

In summary in case of convergence issue the following hierarchical decision tree will be applied

- Binary model including region, agecat, and previousACWY

- Binary model, excluding region, agecat, and previousACWY

- Cochran-Mantel-Haenszel (CMH) method (if strain has 100% killed or 0% killed for ANY treatment)

- VE set to 0% (if strain has 100% killed for both treatment)

5.4.2.3. Distribution of percentages of serogroup B invasive disease strains killed

Not applicable

5.4.2.4. Immune response of MenABCWY, rMenB+OMV NZ and MenACWY

Not applicable

5.5. Safety and reactogenicity

5.5.1. Analysis of safety and reactogenicity planned in the protocol

Distribution of subjects by vaccinations will be summarised by vaccine group for the Enrolled Set. In case of vaccination error, subjects will be analyzed “as treated” (according to the vaccine the subject received).

Analysis sets: Solicited Safety Set (solicited local and systemic adverse events and other solicited adverse events), Unsolicited Safety Set (unsolicited adverse events), and Overall Safety Set.

Endpoint	Statistical Analysis Methods
Primary	**Endpoints description**: The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) adverse events during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. All solicited adverse events will be summarised according to defined severity grading scales, see protocol section 12.5.9.3. Frequencies and percentages of subjects experiencing each adverse event will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic adverse event overall and at each time point will also be presented. Post-vaccination solicited adverse events reported from Day 1 to Day 7 will be summarised for the intervals Day 1-3, Day 4-7, and Day 1-7 by maximal severity and by vaccine group, excluding the 30-minute measurement, which will be summarised separately. The severity of solicited local adverse events, including redness (erythema) at injection site, swelling of skin at injection site, and hardness of skin at injection site will be summarised according to categories based on linear measurement: None (1 to 24mm); Mild (25 to 50mm); Moderate (51 to 100mm); Severe (>100mm). Injection site tenderness and systemic reactions (except fever) occurring up to 7 days after each vaccination at Day 1, Day 61 and Day 181 will be summarised according to "mild", "moderate" or "severe". Each solicited local and systemic adverse event will also be further summarised as "none" versus "any" (for fever the latter will be ≥38.0 °C). Use of antipyretics and analgesics will be summarised by frequency by type of use (prophylactic versus treatment) and percentage of subjects reporting use. Body temperature will be summarised 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 temperatures ≥ 38.0 °C and temperatures ≥ 40.0 °C will also be presented.
	Endpoints description: The frequencies and percentages of subjects with any unsolicited ***AEs*** (including all SAEs), ***AEs*** leading to withdrawal and medically attended ***AEs*** during the 7 and the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. The frequencies and percentages of subjects with SAEs, ***AEs*** leading to withdrawal***, AESIs*** and medically attended ***AEs*** throughout the study period. This analysis applies to all adverse events occurring during the study, judged either as possibly related, or not related to vaccination by the investigator, recorded in AE CRF, with a start date on or after the date of first vaccination. AE starting prior to the first vaccination will only be listed. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class. All reported adverse events, as well as adverse events judged by the investigator as possibly related to study vaccine, will be summarised 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 adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted. Separate summaries will be produced for the following categories: • Serious adverse events. • Adverse events that are possibly related to vaccine. • Adverse events of special interest. • Adverse event leading to withdrawal. • Adverse events leading to a medically attended visit. Data listings of all adverse events will be provided by subject. In addition, adverse events in the categories above will be provided as listed data. Local and systemic AEs will be analyzed by point estimates with associated 95% CIs [Clopper, 1934].

5.5.2. Additional considerations

For analyses of the safety and reactogenicity endpoints, subjects will be analyzed "as treated" according to the actual vaccination a subject received.

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

Analyses of safety objectives will be repeated by age group (10-17 years of age and 18-25 years of age), race, sex, region (US/ ex-US), and with and without a previous MenACWY vaccination (primed and unprimed).

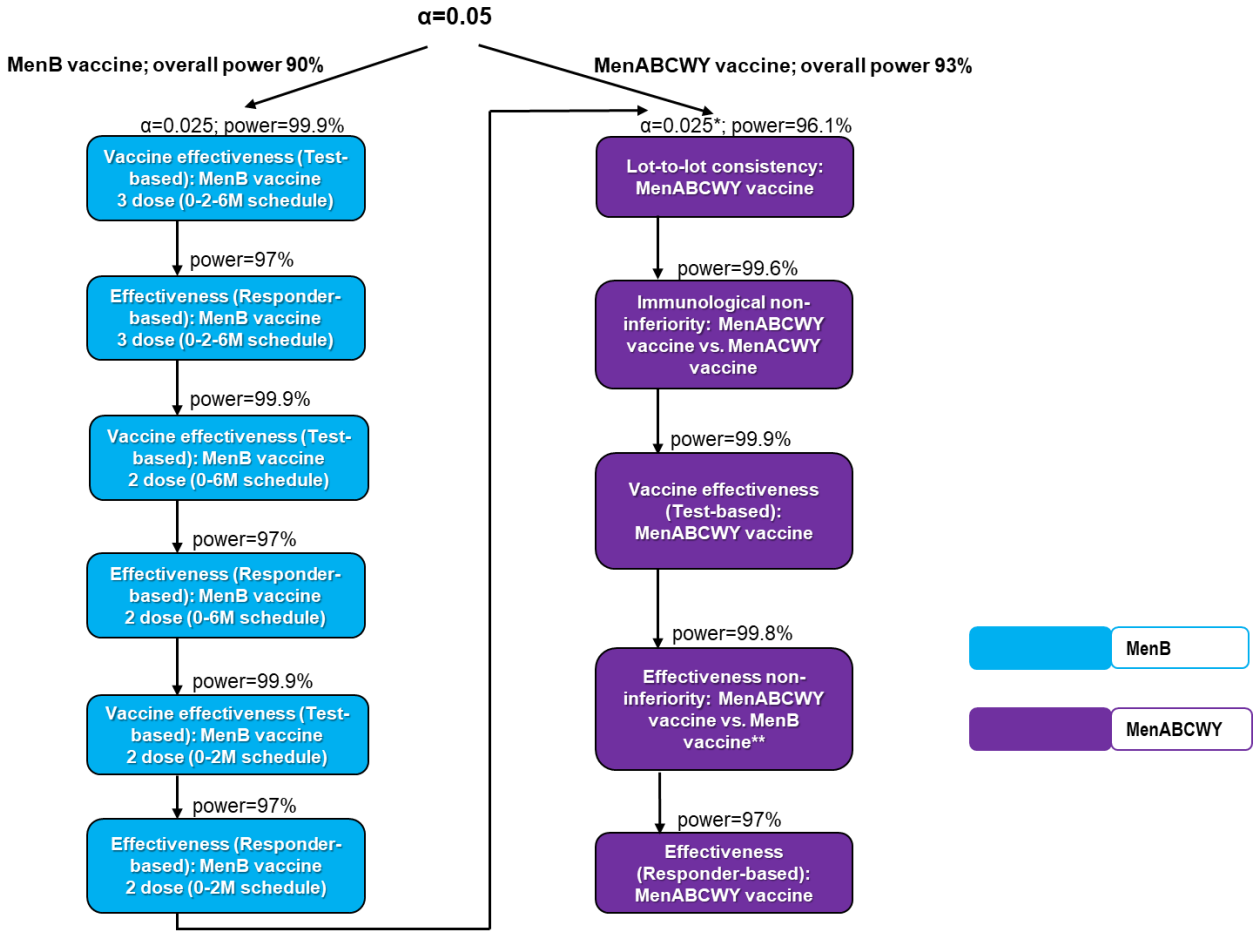
A Table and Listing of COVID-19 AE cases will be provided.

6. ANALYSIS INTERPRETATION

Multiple objectives and endpoints require type I error control. Full alpha (0.05) is split equally (alpha=0.025) between rMenB+OMV NZ objectives and MenABCWY objectives. Furthermore, within rMenB+OMV NZ, as well as within MenABCWY, objectives are tested hierarchically. If the first null hypothesis is rejected, then the testing will continue with the second hypothesis at same alpha. Same for 3rd, 4th, and so forth. Whenever a null hypothesis is not rejected, then the testing will stop.

As the comparator for MenABCWY non inferiority objective for the B component will be the selected schedule of rMenB+OMV NZ as determined in this study, the objectives of rMenB+OMV NZ will be analysed first. Additionally, if all null hypotheses related to rMenB+OMV NZ objectives will be rejected, the alpha (alpha=0.025) will be propagated to the MenABCWY part, and hypotheses related to MenABCWY objectives will be tested at full alpha (alpha=0.05). See Figure 2 for an explanation of the hierarchical testing (top to bottom, the order indicated by the arrows).

Figure 2 Hierarchical testing of hypothesis



* Alpha split equally between rMenB+OMV NZ and MenABCWY vaccine objectives.
If all rMenB+OMV NZ objectives achieved, MenABCWY vaccine objectives will be tested at full alpha.
** If all objectives of rMenB+OMV NZ are met, the comparator will be the 0,2-months schedule. If the 0,2-months objective is not met, and the 0,6-months is met, then the 0,6-months schedule will be the comparator. If the 0,6-months is also not met, then the 0,2,6-months schedule will be the comparator.

Refer to Glossary of terms for definitions of test-based and responder-based vaccine effectiveness.

7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

The final study report will contain at least the final analyses of all primary and secondary endpoints.

7.2. Statistical considerations for interim analyses

No interim analysis is planned for this study

8. CHANGES FROM PLANNED ANALYSES

Not applicable

9. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

The following sections describe additional derivation rules and statistical methods which are not presented in section 10.1.

9.1. Data derivation

Not applicable

9.2. Statistical Method

Not applicable

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

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

10.1.1. Attributing events to vaccine doses

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

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

10.1.2. Handling of missing data

10.1.2.1. Dates

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

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

The following exceptions apply:

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

year. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that year.

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

10.1.2.2. Laboratory data

Missing laboratory results (including immunological data) will not be replaced.

10.1.2.3. Daily recording of solicited adverse events

10.1.2.3.1. Studies with electronic diaries

For studies using electronic diaries for the collection of solicited adverse events, a solicited adverse events will be considered present only when a daily recording of grade 1 or more is present.

10.1.2.4. Unsolicited adverse events

Unsolicited adverse event summaries are including serious adverse events unless specified otherwise.

Missing severity, relationship with study vaccine, and outcome of unsolicited adverse events will not be replaced and will appear as 'UNKNOWN' in all statistical output.

10.1.3. Data derivation

10.1.3.1. Age at vaccination in days

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

Age = date of vaccination minus date of birth

10.1.3.2. Age at vaccination in months

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

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

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

10.1.3.3. Age at vaccination in years

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

DOB = 10SEP1983, Date of vaccination = 09SEP2018 -> Age = 34 years

DOB = 10SEP1983, Date of vaccination = 10SEP2018 -> Age = 35 years

10.1.3.4. Weight

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

Weight in kilograms = Weight in pounds / 2.2

10.1.3.5. Height

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

Height in centimeters = Height in inches x 2.54

10.1.3.6. Body mass index (BMI)

BMI will be calculated as follows:

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

10.1.3.7. Temperature

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

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

10.1.3.8. Numerical serology results

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

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

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

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

10.1.3.10. Onset day

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

10.1.3.11. Duration of events

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

10.1.3.12. Counting rules for combining solicited and unsolicited adverse events

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

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

10.1.3.13. Counting rules for occurrences of solicited adverse events

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

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with:

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

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

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

10.1.4.2. Differences in percentages

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

10.1.4.3. Demographic/baseline characteristics statistics

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

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

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

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

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

10.1.4.4. Serological summary statistics

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

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

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

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

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

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

10.1.5.2. Standardized asymptotic confidence intervals around differences in proportions

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

10.2. TFL TOC

The Tables Figures and Listings (TFL) Table of Contents (TOC) which itemizes the planned list of TFL and their associated lay-out is developed as a separate document.

10.3. Glossary of terms

End of Study (EoS) **(Synonym of End of Trial)**	For studies with collection of human biological samples and/or imaging data, the EoS is defined as Last subject last visit (T10). or Last testing results released of samples collected at Visit 6* * In this case EoS must be achieved no later than 8 months after LSLV.
Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.
Responder-based vaccine effectiveness:	The enc-hSBA methodology involves testing the serum samples from each individual subject against a subset of around 35 strains randomly chosen from the overall panel of 110 meningococcus B US strains. Responder-based vaccine effectiveness is assessed based on the percentage of subjects considered responders, i.e., subjects whose serum kills the majority (≥70% in this study) of the tested strains following vaccination.
Test-based vaccine effectiveness:	The enc-hSBA methodology involves testing the serum samples from each individual subject against a subset of around 35 strains randomly chosen from the overall panel of 110 meningococcus B US strains. Test-based vaccine effectiveness is assessed based on the overall percent of individual positive tests following vaccination and represents the reduction in risk compared to the placebo.

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GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A phase III, randomized, controlled, observer-blind study to demonstrate effectiveness, immunogenicity and safety of GSK's meningococcal Group B and combined ABCWY vaccines when administered to healthy adolescents and young adults.
eTrack study number and Abbreviated Title	205416 [MENB REC 2ND GEN-038 (V72_72)]
Scope:	All data pertaining to the above study
Date of Statistical Analysis Plan	Final: 25 Mar 2022

APP 9000058193 Statistical Analysis Plan Template V4 (Effective date: 3June2019)

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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
Eli Type	Internal database code for type of elimination code
ELISA	Enzyme-linked immunosorbent assay
EOS	End of Study
ES	Exposed Set
FAS	Full Analysis Set
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titre
GSK	GlaxoSmithKline
LL	Lower Limit of the confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
PCD	Primary completion Date
PPS	Per-Protocol Set
RR	Relative Risk
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
TFL	Tables Figures and Listings
TOC	Table of Contents

1. DOCUMENT HISTORY

Date	Description	Protocol Version
25 July 2019	First version	Amendment 1: 23 MAY 2019
15 June 2020	Amendment 1	Amendment 2: 18 MAR 2020
25 Mar 2022	Amendment 2	Amendment 4: 12 MAY 2021

2. OBJECTIVES/ENDPOINTS

Table 1 Study objectives and endpoints

Objectives	Endpoints
Primary	
Vaccine effectiveness (Test-based): rMenB+OMV NZ To demonstrate the effectiveness of the rMenB+OMV NZ vaccine against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity using enc-hSBA at 1 month after the 3-dose (0,2,6-months) and 2-dose (0,6-months; 0,2-months) vaccination series when compared to 1 month after the MenACWY vaccination. *Criterion* *Lower limit (LL) of the two-sided 97.5% confidence interval (CI) for vaccine effectiveness is above 65% against a randomly selected strain panel between the:* • *MenB_0_2_6 and ACWY groups (for 0,2,6-months schedule)* • *MenB_0_6 and ACWY groups (for 0,6-months schedule),* • *MenB_0_2_6 and ACWY groups (for 0,2-months schedule)*	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at 1 month after the: • 3-dose vaccination series in MenB_0_2_6 group (Day 211, Month 7) • 2-dose vaccination series in MenB_0_6 group (Day 211, Month 7), and • 2-dose vaccination series in MenB_0_2_6 group (Day 91, Month 3) • 1 month after the MenACWY vaccination in ACWY group (Day 31, Month 1).
Effectiveness (Responder-based): rMenB+OMV NZ To demonstrate the effectiveness of the rMenB+OMV NZ vaccine by assessing the percentages of subjects whose sera kill ≥70% of strains tested using enc-hSBA at 1 month after the 3-dose (0,2,6-months) and 2-dose (0,6-months; 0,2-months) vaccination series of the rMenB+OMV NZ. *Criterion:* *LL of the two-sided 97.5% CI for the percentages of subjects whose sera kill ≥70% of strains is above 65%, tested for:* • *MenB_0_2_6 group (for 0,2,6-months schedule)* • *MenB_0_6 group (for 0,6-months schedule),* • *MenB_0_2_6 group (for 0,2-months schedule)*	The percentages of subjects whose sera kill ≥70% of the strains tested using enc-hSBA, at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group), • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group)
The 3 vaccine schedules will be tested for both, test-based and responder-based, in a hierarchical way (starting from 0-2-6, to 0-6 and 0-2). Refer to Protocol Section 10.1 for details on continuing the evaluation.	

Objectives	Endpoints
Lot-to-lot consistency: MenABCWY vaccine To demonstrate lot-to-lot consistency of the immune responses of 3 lots of the MenACWY component of the MenABCWY vaccine, as measured by hSBA GMTs directed against serogroups A, C, W and Y at 1 month after last vaccination (0,6-months). *Criterion:* *The two-sided 97.5% CIs^ for the ratio of hSBA GMTs of antibodies against serogroups A, C, W and Y are within the [0.5;2.0] equivalence interval for each pair of lots.*	GMTs directed against serogroups A, C, W and Y for each lot (ABCWY-1 group, ABCWY-2 group, ABCWY-3 group) at 1 month after the last vaccination (Day 211, Month 7)
Immunological non-inferiority: MenABCWY vaccine vs. MenACWY vaccine To demonstrate the immunological non-inferiority of the MenABCWY vaccine compared to the MenACWY vaccine as measured by the percentages of subjects achieving a 4-fold rise in hSBA titres against *N. meningitidis* serogroups A, C, W and Y at 1 month after the last MenABCWY vaccination (0,6-months) and 1 month after the MenACWY vaccination. *Criterion:* *LL of the 2-sided 97.5% CI^ for the group difference in percentages of subjects achieving a 4-fold rise* in hSBA titres is above -10%.*	The percentages of subjects with 4-fold rise* in hSBA titres against *N. meningitidis* serogroups A, C, W and Y at 1 month after the: • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • 1 month after the MenACWY vaccination for the ACWY group (Day 31, Month 1) relative to baseline (Day 1, Month 0).
Vaccine effectiveness (Test-based): MenABCWY vaccine To demonstrate the effectiveness of the MenABCWY vaccine against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains as measured by enc-hSBA at 1 month after the last MenABCWY vaccination (0,6-months) when compared to 1 month after the MenACWY vaccination. *Criterion:* *LL of the two-sided 97.5% CI^ for vaccine effectiveness is above 65% against a randomly selected strain panel between the ABCWY group (pooled lots) and the ACWY group.*	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at 1 month after the: • last vaccination for the ABCWY group (pooled) (Day 211, Month 7), and • 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1).
Effectiveness non-inferiority: MenABCWY vaccine vs. rMenB+OMV NZ vaccine To demonstrate the non-inferiority of the effectiveness of the MenABCWY vaccine (0,6-months schedule) compared to the rMenB+OMV NZ vaccine (0,2,6-months or 0,6-months or 0,2-months)† in terms of percentage of samples with bactericidal serum activity using enc-hSBA against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains. *Criterion:* *LL of the two-sided 97.5% CI^ for the difference in percentages of samples with bactericidal serum activity using enc-hSBA against a randomly selected panel of*	The percentages of samples with bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains at 1 month after the: • last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • 3-dose vaccination series of rMenB+OMV vaccine (Day 211, Month 7 in MenB_0_2_6 group) or 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) or 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group)†

Objectives	Endpoints
endemic US N. meningitidis serogroup B invasive disease strains is above -5% at 1 month after: • *the last vaccination in ABCWY group (pooled lots) (for 0,6 months schedule), and* • *The last vaccination in MenB_0_2_6 group (for 0,2,6-months schedule) or the last vaccination in MenB_0_6 group (for 0,6-months schedule) or the second vaccination in MenB_0_2_6 group (for 0,2-months schedule*	
Effectiveness (Responder-based): MenABCWY vaccine To demonstrate the effectiveness of MenABCWY vaccine by assessing the percentages of subjects whose sera kill ≥70% of strains tested using enc-hSBA at 1 month after the last vaccination of MenABCWY (0,6-months). *Criterion:* *LL of the two-sided 97.5% CI^ for the percentages of subjects whose sera kill ≥70% of strains tested for MenABCWY is above 65%.*	The percentages of subjects whose sera kill ≥70% of the strains tested using enc-hSBA, at 1 month after the last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7).
Safety To evaluate the safety and reactogenicity of the MenB, MenABCWY, and the MenACWY vaccines	• The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [body temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) adverse events (AEs) during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. • The frequencies and percentages of subjects with any unsolicited AEs (including all SAEs, AEs leading to withdrawal, AESIs and medically attended AEs) during the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. • The percentages of subjects with SAEs, AEs leading to withdrawal, AESIs and medically attended AEs throughout the study period [Month 0 to Month 18].
Secondary	
To demonstrate the immunological non-inferiority of the MenABCWY vaccine compared to the rMenB+OMV NZ vaccine as measured by the percentages of subjects achieving a 4-fold rise in hSBA titres against *N. meningitidis* serogroup B indicator strains at 1 month after the last MenABCWY vaccination (0,6-months schedule) and 1 month after the rMenB+OMV NZ vaccination (0,2,6-months or 0,6-months or 0,2-months) † *Criterion:* *Non-inferiority will be demonstrated if the LL of the 2-sided 95% CI for the group difference in percentage of*	The percentages of subjects with 4-fold rise** in hSBA titres against *N. meningitidis* serogroup B indicator strains at 1 month after the: • last MenABCWY vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • 3-dose vaccination series of rMenB+OMV vaccine(Day 211, Month 7 in MenB_0_2_6 group) or 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) or 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group) † relative to baseline (Day 1, Month 0).

Objectives	Endpoints
*subjects achieving a 4-fold rise** in hSBA titres against N. meningitidis serogroup B indicator strains is above -10%.*	
To assess the effectiveness of the rMenB+OMV NZ and MenABCWY vaccines against each of the randomly selected endemic US *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series when compared to 1 month after the MenACWY vaccination.	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group) • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • MenACWY vaccination (Day 31, Month 1 in ACWY group).
To describe the distribution of subjects by percentages of serogroup B invasive disease strains killed using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series of rMenB+OMV NZ and MenABCWY vaccines.	The percentages of serogroup B invasive disease strains killed using enc-hSBA in each subject at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7)
To assess the immune response to the rMenB+OMV NZ (0,2,6-months, 0,6-months and 0,2-months) and MenABCWY (0,6-months) vaccines against *N. meningitidis* serogroup B indicator strains at pre-vaccination (Day 1, Month 0) and at 1 month after the last MenABCWY vaccination and at 1 month after the second and third vaccination of rMenB+OMV NZ.	The immune response to the rMenB+OMV NZ and ABCWY vaccines will be evaluated by measuring bactericidal activity against *N. meningitidis* serogroup B indicator strains as following: *1. The percentages of subjects with hSBA titres ≥ lower limit of quantitation (LLOQ) for each (individual response) and all (composite response) serogroup B indicator strains at baseline (Day 1, Month 0) and at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *2. The percentages of subjects with 4-fold rise** in hSBA titres at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 90, Month 3 in MenB_0_2_6 group), and

Objectives	Endpoints
	• last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *relative to baseline (Day 1, Month 0).* *3. hSBA GMTs at baseline (Day 1, Month 0) and at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *4. hSBA GMRs at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *relative to the baseline (Day 1, Month 0).*
To assess the immune response to MenABCWY (0,6-months schedule) and MenACWY (single dose) vaccines against *N. meningitidis* serogroups A, C, W and Y, at pre-vaccination (Day 1, Month 0) and at 1 month after the first and the last MenABCWY vaccination and 1 month after the MenACWY vaccination.	*1. The percentage of subjects with hSBA titres ≥ LLOQ for serogroups A, C, W and Y at baseline (Day 1, Month 0) and:* • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1). *2. The percentage of subjects with 4-fold rise* in hSBA titres at 1 month after the:* • first vaccination (Day 31, Month 1) for the ABCWY group (pooled lots) compared to the MenACWY vaccination in the ACWY group (Day 31, Month 1) *relative to baseline (Day 1, Month 0).* *3. hSBA GMTs against N. meningitidis serogroups A, C, W and Y* at baseline (Day 1, Month 0) and: • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1). *4.hSBA GMRs against N. meningitidis serogroups A, C, W and Y at:* • 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots) as compared to baseline (Day 1, Month 0), and

Objectives	Endpoints
	• 1 month after the single MenACWY vaccination in the ACWY group (Day 31, Month 1) as compared to baseline (Day 1, Month 0). *5.The total IgG as measured by ELISA GMCs against serogroups A, C, W and Y* at baseline (Day 1, Month 0) and*:* • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1).

Abbreviations: ELISA = enzyme-linked immunosorbent assay; Enc-hSBA = endogenous complement human serum bactericidal assay; GMC = geometric mean concentrations; GMT = geometric mean titre; GMR = geometric mean ratio; CI = confidence interval; hSBA = human serum bactericidal assay; LOD: limit of detection; LLOQ = lower limit of quantitation; LL = lower limit; AE = Adverse event; SAE = Serious adverse event; AESI = Adverse event of special interest

N.meningitidis serogroup B indicator strains = M14459, 96217, M07-0241084 and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively. The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented either in a protocol amendment or in the clinical report.

Refer to Protocol Section 10 for details on evaluation of objectives and sample size justification. Refer to Glossary of terms for definitions of test-based and responder-based effectiveness

^ If the co-primary effectiveness objectives for rMenB+OMV NZ are met, then all objectives for MenABCWY will be evaluated at 95% CI. Refer to Protocol Section 10.1 for details

† If all objectives of rMenB+OMV NZ are met, the comparator will be the 0,2-months schedule. If the 0,2-months objective is not met, and the 0,6-months is met, then the 0,6-months schedule will be the comparator. If the 0,6-months is also not met, then the 0,2,6-months schedule will be the comparator.

*For the Men A, C, W, Y evaluation, the 4-fold rise is defined as:

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

**For the MenB evaluation, the 4-fold rise per each indicator strain is defined as:

- a post-vaccination‡ hSBA titre ≥4 times the LOD for subjects with a pre-vaccination hSBA titre <LOD
- a post-vaccination‡ hSBA titre ≥4 times the LLOQ for subjects with a pre-vaccination hSBA titre ≥LOD and <LLOQ, and
- a post-vaccination‡ hSBA titre ≥4 times the pre-vaccination hSBA titre for subjects with a pre-vaccination hsBA titre ≥LLOQ

‡ = post-2nd vaccination for 0,6 and 0,2 schedule and post-3rd vaccination for 0,2,6 schedule.

3. STUDY DESIGN

3.1. Scientific rationale for study design

As the rMenB+OMV NZ licensure in the US was issued through accelerated approval, the FDA has requested to demonstrate the effectiveness of the vaccine against an extended panel of serogroup B meningococcal strains (MenB) as a post-marketing commitment in US adolescents and young adults, thus confirming that the vaccine can protect against diverse meningococcal B strains prevalent in the United States.

The availability of a pentavalent meningococcal vaccine in a single administration would however reduce the number of injections and could increase coverage for meningococcal disease caused by *N. meningitidis* serogroups A, B, C, W, and Y worldwide. GSK's investigational MenABCWY combination vaccine is intended to protect against 5 of the most prevalent serogroups of *Neisseria meningitidis* (A, B, C, W, Y) in humans.

Hence, along with the licensed MenB vaccine (*Bexsero*), this Phase III study will also assess the safety, effectiveness, and immunogenicity of the investigational MenABCWY vaccine.

Rationale for effectiveness assessment

As mentioned above, one of the primary purposes of this study is to evaluate the effectiveness of 2 or 3 doses of rMenB+OMV NZ and of 2 doses of the MenABCWY vaccines in healthy adolescents and young adults by measuring the bactericidal activity against 110 endemic US *N. meningitidis* serogroup B strains using an endogenous complement human Serum Bactericidal Assay (enc-hSBA). Sera from the ACWY group receiving the MenACWY vaccine will also be tested against serogroup B meningococcal strains by enc-hSBA as a control for test-based effectiveness assessment. The overall vaccine effectiveness (VE) against all 110 strains combined will be computed by means of a generalised linear model. For additional details see statistical analysis section of the Clinical Study Protocol (Protocol Section 10).

Rationale for lot-to-lot consistency assessment

MenABCWY is a reconstituted vaccine with the lyophilised 'ACWY component' and liquid rMenB+OMV NZ. The MenB component has the same formulation as the commercial *Bexsero*. To demonstrate that the lots of the investigational MenABCWY vaccine are adequately representative of the formulation intended for marketing, equivalence will be assessed for 3 different lots of the ACWY component of the ABCWY vaccine.

Rationale for non-inferiority assessment of MenABCWY vs MenACWY and rMenB+OMV NZ

The study aims to also demonstrate that the investigational combination MenABCWY vaccine is not inferior to a licensed MenACWY vaccine (*Menveo*) and a licensed MenB vaccine (*Bexsero*) which are part of the current standards of care in the US for prevention of invasive disease caused by *N. meningitidis* serogroups A, C, W, Y and by *N. meningitidis* serogroup B, respectively.

Rationale for blood volume collected:

In order to provide the necessary serum volume for the bactericidal assays (enc-hSBA and/ or hSBA(s)), 25 mL whole blood will be collected at Visit 2, Visit 4 and Visit 6. At pre-vaccination (Visit 1), 20 mL whole blood will be collected to provide the necessary serum volume for the hSBA.

Blood samples are taken from all subjects irrespective of the testing status in order to maintain the study blind. Refer to Protocol Section 8.4.2.1 for further details.

Rationale for the selected vaccination schedules

rMenB+OMV NZ: This study aims at demonstrating the VE of the rMenB+OMV NZ vaccine administered as 2-dose vaccine, either with a shorter interval (0,2-months) or a prolonged interval (0,6-months) between doses. A 3-dose schedule has been also added to better characterise the VE.

Note: The rMenB+OMV NZ in the ACWY group is administered in a 0,1-months schedule. This interval is within the recommendations in the summary of product characteristics of *Bexsero* and helps in maintaining the blind. No objectives are associated with this schedule of rMenB+OMV NZ.

MenABCWY: A number of different vaccine formulations were evaluated in MenABCWY Phase I and II clinical studies. The formulation with the same active ingredient composition as the rMenB+OMV NZ (*Bexsero*) and MenACWY (*Menveo*) vaccines was chosen as the final formulation of the investigational MenABCWY vaccine. Two doses administered 6 months apart (0,6-months) is considered the optimal dosing schedule, based on serogroup B immunogenicity results from MenABCWY Phase II clinical studies.

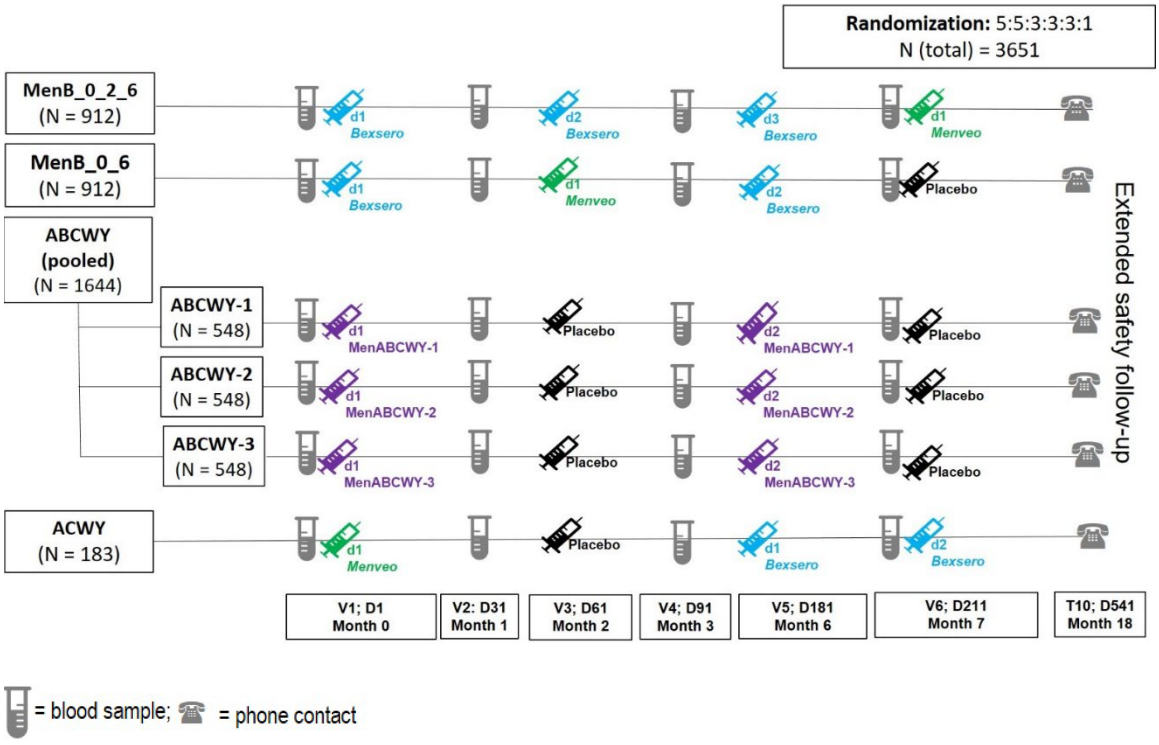
MenACWY: As a comparator for serogroup A, C, W, and Y vaccine effectiveness and immune responses, a single dose of MenACWY vaccine is administered to subjects in the ACWY group. To conform with the standard of care (also in alignment with current ACIP routine immunisation recommendations in US), subjects in the MenB_0_2_6 and MenB_0_6 groups will also receive a dose of MenACWY at Day 211 and Day 61, respectively.

3.1.1. Rationale for the use of placebo

For this study, a placebo (saline solution) will be administered as presented in Figure 1. A placebo is the only available option to minimize possible introduction of reporting bias in collecting information about AEs and to ensure the same number of vaccinations are administered to subjects assigned to either of the six study groups.

3.2. Overall design

Figure 1 Study design overview



N = number of subjects; d = dose; V = visit; D = day; T=Telephone call
Refer to Protocol Table 3 for details on all visits
Note: Home visits may be performed only by sites authorised (as per local regulations and sponsor agreement), with approved site level standard operating procedures (SOP) provided that the compliance with protocol procedures are ensured.

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the schedule of activities (Protocol Section 2), are essential and required for study conduct.

- Type of study: self-contained

- Experimental design: This is a phase III, randomised, controlled, observer-blind, multi-center study to evaluate effectiveness, immunogenicity and safety of rMenB+OMV NZ and MenABCWY vaccines. A total of 3651 healthy adolescents and young adults aged 10-25 years will be enrolled and randomised (5:5:3:3:3:1 ratio) to one of the six parallel study groups:

  - **MenB_0_2_6 group***: subjects will receive 3 doses of rMenB+OMV NZ at Day 1, Day 61 and Day 181 (0, 2 and 0,2,6-months schedule). These subjects will receive 1 dose of the MenACWY vaccine at Day 211**.
  - **MenB_0_6 group**: subjects will receive 2 doses of rMenB+OMV NZ at Day 1 and Day 181 and 1 dose of MenACWY vaccine at Day 61 (rMenB+OMV NZ, 0,6-months schedule). These subjects will receive 1 dose of placebo at Day 211**.
  - **ABCWY-1**: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 1 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211**.
  - **ABCWY-2**: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 2 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211**.
  - **ABCWY-3**: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 3 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211**.
  - **ACWY group**: subjects will receive 1 dose of MenACWY vaccine at Day 1, 1 dose of placebo at Day 61 and 2 doses of rMenB+OMV NZ at Day 181 and Day 211**.

  * MenB_0_2_6 group will also be evaluated for objectives pertaining to 0,2-months vaccination schedule.

  Note 1: A MenB lot will be used for the pre-filled syringe component of the MenABCWY vaccine.

  Note 2: The groups ABCWY-1, ABCWY-2, ABCWY-3 will be pooled into a single group, ABCWY (pooled lots) (except for analysis of lot to lot consistency).

  ** Note 3: In order to let the subjects in MenB_0_2_6 group receive a dose of MenACWY vaccine and for subjects in ACWY group to receive the second dose of rMenB+OMV NZ in line with the vaccine as standard of care (also in line with the Advisory Committee on Immunization Practices (ACIP) recommendations in the US [ACIP, 2011]), the subjects in these groups will receive a vaccination of MenACWY and rMenB+OMV NZ vaccines, respectively, on Day 211 (Visit 6) after completion of the post-vaccination 3 blood sampling. To maintain the blinding of the study, subjects in the rest of the groups (MenB_0_6, ABCWY-1, ABCWY-2 and ABCWY-3) will receive a dose of Placebo. All these vaccines/ product administered at Day 211 are not associated with any study objectives/ endpoints (Safety assessment

conducted after 1 dose of rMenB+OMV NZ in the ACWY group at Day 181 is to maintain the blind of the study).

- Duration of the study: The study duration is approximately 18 months for each subject.
- Primary completion Date (PCD): T10; Day 541.

Refer to Glossary of terms for the definition of PCD.

- End of Study (EoS): the date of release of the last testing results, to be achieved not later than 8 months after Last Subject Last Visit (LSLV) (LSLV = T10; Day 541). If the completion of testing occurs prior the completion of the LSLV the latter date defines the end of study visit.

Refer to Glossary of terms for the definition of EoS.

- Study groups:

Table 2 Study groups and treatment foreseen in the study

Study Groups	Number of subjects	Age (Min-Max)	Treatment name	Vaccine/Product name
MenB_0_2_6	912	10 – 25 y	*Bexsero* (Injection)	rMenB+OMV NZ
			Menveo (Injection)	MenACWY
MenB_0_6	912		*Bexsero* (Injection)	rMenB+OMV NZ
			Menveo (Injection)	MenACWY
			Placebo (Injection)	NaCl
ABCWY-1	548		MenABCWY (with Lot 1 of ACWY) (Injection)	MenABCWY-1
			Placebo (Injection)	NaCl
ABCWY-2	548		MenABCWY (with Lot 2 of ACWY) (Injection)	MenABCWY-2
			Placebo (Injection)	NaCl
ABCWY-3	548		MenABCWY (with Lot 3 of ACWY) (Injection)	MenABCWY-3
			Placebo (Injection)	NaCl
ACWY	183		*Menveo* (Injection)	MenACWY
			Placebo (Injection)	NaCl
			Bexsero (Injection)	rMenB+OMV NZ

Table 3 Overview of study design: Vaccination and Blood Draw Schedule

Visits **Study Day**	**Visit 1** **Day 1**	Visit 2 Day 31	**Visit** 3 **Day 61**	**Visit** 4 **Day 91**	**Visit** 5 **Day 181**	**Visit** 6 **Day 211**
Group **MenB_0_2_6** **N=912**	Pre-vacc Blood sample rMenB+OMV NZ	Post-vacc 1 Blood sample	rMenB+OMV NZ	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample MenACWY
Group **MenB_0_6** **N=912**	Pre-vacc Blood sample rMenB+OMV NZ	Post-vacc 1 Blood sample	MenACWY	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample Placebo
Group **ABCWY-1** **N=548**	Pre-vacc Blood sample MenABCWY-1	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-1	Post-vacc 3 Blood sample Placebo
Group **ABCWY-2** **N=548**	Pre-vacc Blood sample MenABCWY-2	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-2	Post-vacc 3 Blood sample Placebo
Group **ABCWY-3** **N=548**	Pre-vacc Blood sample MenABCWY-3	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-3	Post-vacc 3 Blood sample Placebo
Group **ACWY** **N=150**	Pre-vacc Blood sample MenACWY	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample rMenB+OMV NZ

N = number of subjects; Pre-vacc = pre-vaccination; Post-vacc = post-vaccination

- Treatment allocation: At Day 1, prior to the study vaccination, subjects will be randomised to 1 of the 6 study groups according to a 5:5:3:3:3:1 ratio.
- Blinding: Observer-blind. Kindly refer to Protocol Section 7.3 for details on blinding and unblinding procedures.
- Sampling schedule:
  - A total of 4 blood samples* will be collected from each subject at Day 1 (pre-vaccination blood sample; approximately 20 mL), at Day 31 (post-vaccination 1 blood sample; approximately 25 mL), at Day 91 (post-vaccination 2 blood sample; approximately 25 mL) and at Day 211 (post-vaccination-3 blood sample; approximately 25 mL).
  - Urine sampling: Urine samples for pregnancy testing will be collected from female subjects of child-bearing potential at Visit 1 (Day 1), Visit 3 (Day 61), Visit 5 (Day 181) and Visit 6 (Day 211) prior to the vaccination.

  * Insufficient blood volume may lead to test cancellation and jeopardise the statistical power. Hence, every effort must be done to collect blood volume as per protocol requirements.
- Data collection: standardised Electronic Case Report Form (eCRF). Solicited symptoms will be collected using a subject Diary (electronic Diary [eDiary]).
- Safety monitoring: Regular safety follow-up will be done through telephone calls (T). There will also be an extended safety follow-up (ESFU) phone call 12 months post-vaccination 3 (Day 181; Visit 5). This ESFU phone call will also mark the study conclusion. Refer to Protocol Table 3 and Protocol Section 8.5.3 for details on the safety follow-up.

3.3. Number of subjects

A total of 3651 subjects will be randomised in a ratio of 5:5:3:3:3:1; 912 each in MenB_0_2_6 and MenB_0_6 groups, 548 in each ABCWY groups and 183 in ACWY group. Assuming a 25% drop out rate, this should provide approximately 684 evaluable subjects in each of the MenB groups, 411 evaluable subjects in each of the ABCWY groups and 137 evaluable subjects in the ACWY group.

Refer to Protocol Section 10.1 for a detailed description of the criteria used in the determination of sample size.

Withdrawals will not be replaced.

3.4. Subject and study completion

A subject is considered to have completed the study, if the subject is available for the concluding contact (T10; Day 541) as described in the protocol.

Global completion of the study is required in order to provide enough subjects as defined in Protocol Section 10.1 Sample Size Determination.

4. ANALYSIS SETS

4.1. Definition

For purposes of analysis, the following analysis sets are defined:

4.1.1. Enrolled Set

Subject/ Subject for whom parent(s)/LAR's agreed to participate in a clinical study after completion of the informed consent process, who meet screening/eligibility criteria and randomized and/or received study intervention or undergone an invasive procedure.

4.1.2. Exposed Set

All subjects who received at least 1 dose of the study treatment. The allocation in a group is done in function of all administered treatments.

4.1.3. Full Analysis Set

All subjects who received at least 1 dose of the study treatment and have post-vaccination effectiveness or immunogenicity data.

4.1.4. Per Protocol Set

All subjects in the Full Analysis Set minus subjects with protocol deviations that lead to exclusion from the Per Protocol Set.

4.1.5. Solicited Safety Set

All subjects who received at least 1 dose of the study treatment (Exposed Set) who have solicited safety data beyond 30 minutes post vaccination.

4.1.6. Unsolicited Safety Set

All subjects who received at least 1 dose of the study treatment (Exposed Set) that report unsolicited AEs/report not having unsolicited AEs.

4.1.7. Overall Safety Set

All subjects that belong to the Unsolicited safety or/and to the Solicited safety set.

4.2. Criteria for eliminating data from Analysis Sets

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

4.2.1. Elimination from Exposed Set (ES)

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

4.2.2. Elimination from Per protocol Set (PPS)

4.2.2.1. Excluded subjects

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

Table 4 Elimination code and condition to exclude a subject from the PPS analysis

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
800	Fraudulent data	All	All
900	Invalid informed consent	All	All
1030	Study vaccine not administered at all	All	All
1050	Randomization failure	Visit 1, 3, 5	All
1060	Randomization code was broken	All	All
1070.1	Subjects got vaccinated with the correct vaccine but containing a lower volume	Visit 1, 3, 5	All
1070.2	Vaccination not according to protocol	Visit 1, 3, 5	All
1080	Vaccine temperature deviation	Visit 1, 3, 5	All
1090	Expired vaccine administered	Visit 1, 3, 5	All
1500.1	Other deviation from study procedures not able to classified under any other categories	All	All
1500.2	Any other GCP non-compliance not able to classified under any other categories	All	All
2010	Protocol violation (inclusion/exclusion criteria)	All	All
2040	Administration of any medication forbidden by the protocol	Visit 1, 3, 5	All
2050	Not withdrawn after developing withdrawal criteria other than prohibited concomitant vaccination/medication (medical condition forbidden)	All	All
2060	Concomitant infection related to the vaccine which may influence immune response (only meningococcal infection)	All	All
2080	Subjects did not comply with vaccination schedule	Visit 3, 5	All

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
2090	Subjects did not comply with blood sample schedule	Visit 2, 4, 6	All
2100	Serological results not available post-vaccination for all tests	Visit 2, 4, 6	All
2120	Obvious incoherence or abnormality or error in data related to testing	Visit 2, 4, 6	All
2130	Biological sample specimen procedures not compliant with protocol	Visit 2, 4, 6	All

4.2.3. Elimination from unsolicited and solicited safety set

4.2.3.1. Excluded subjects

4.2.3.1.1. Unsolicited safety set

Code 1030 (Study vaccine not administered at all), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1150 (no post-vaccination safety data) will be used for identifying subjects eliminated from the unsolicited safety set.

4.2.3.1.2. Solicited safety set

Code 1030 (Study vaccine not administered at all), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1160 (no post-vaccination solicited safety data) will be used for identifying subjects eliminated from the solicited safety set.

5. STATISTICAL ANALYSES

Standard data derivation rules and statistical methods are described in section 10.1 while the study specific data derivation rules and stat methods are described in section 9.

5.1. Disposition of subjects

5.1.1. Analysis of disposition of subjects planned in the protocol

Number of subjects enrolled, vaccinated subjects (at least 1 vaccination, full vaccination course), reason for early withdrawal, FAS, and PPS will be described by vaccine group.

5.1.2. Additional considerations

Not applicable

5.2. Demography and baseline characteristics analyses

5.2.1. Analysis of demography and baseline characteristics planned in the protocol

Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age, height, weight, and body mass index (BMI) at enrolment will be calculated overall and by vaccine group.

Distributions of subjects by sex, race, ethnic origin will be summarised overall and by vaccine group.

5.2.2. Additional considerations

A summary table of important protocol deviations related to COVID-19 will be provided. Also, a listing will be produced.

5.3. Primary effectiveness and immunogenicity

5.3.1. Analysis of primary effectiveness and immunogenicity planned in the protocol

Refer to Glossary of terms for definitions of test-based and responder-based vaccine effectiveness. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then all objectives for MenABCWY will be evaluated at 95% CI (Sections 5.3.1.7 through 5.3.1.11, ref Protocol Section 10.1).

5.3.1.1. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Analysis set: Per-protocol set (PPS) will be the primary analysis population

Statistical method: The VE is defined as 1- RR= (1- percentage of samples without bactericidal serum activity at 1:4 dilution in MenB group / percentage of samples without bactericidal serum activity at 1:4 dilution in the ACWY group) x100% and it will be analyzed using a generalised linear model with vaccine group, strain, and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) as independent variables. Furthermore, a repeated statement will be used to estimate the variance of the RR including correlation within subject's responses to different strains. If the statistical model does not converge due to (one of) the factor(s), a model without this/these factor(s) will be fitted instead. The response variable of the model will be the Bernoulli distributed outcome without bactericidal activity at a 1:4 dilution (i.e. response is 1 if titre < 4, and 0 if titre ≥ 4), at 1 month after the last vaccination (Month 7) in the MenB group and at Month 1 for the ACWY group. Each subject will contribute with approximately 35 measures to this analysis, each of the measures corresponding to the response variable to one of the 35 strains randomly assigned to be tested with the samples available for that specific subject.

In order to obtain the VE measure which is a measure based on the relative risk (RR), a generalised linear model will be used with the Binary distribution and link function log in order to compute the log RR and the corresponding 97.5% CI. The obtained values will be exponentiated to obtain the RR and the corresponding 97.5% CI. The VE will be computed as 100% x (1 – RR). Effectiveness of rMenB+OMV NZ (0,2,6-months schedule) will be demonstrated if the lower limit of the two-sided 97.5% CI for VE between MenB and the ACWY group is above 65%.

5.3.1.2. Effectiveness (Responder-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Analysis set: FAS will be the primary analysis population.

Statistical method: The percentage of responders (see definition in Glossary of terms) and the corresponding exact two-sided 97.5% CI based on Clopper-Pearson method will be calculated [Clopper, 1934].

The objective is to demonstrate that the lower limit of the 97.5% CI for the percentage of responders is higher than 65%.

5.3.1.3. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 5.3.1.1

5.3.1.4. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 5.3.1.2

5.3.1.5. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 5.3.1.1

5.3.1.6. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 5.3.1.2

5.3.1.7. Lot-to-lot consistency: MenABCWY - ACWY component

Analysis set: The analysis of lot-to-lot consistency will be based on the PPS.

Statistical method: For each of the three ABCWY lots (Lots 1, 2 and 3 of the MenACWY component of the ABCWY vaccine), GMTs and 97.5% CIs will be calculated by exponentiating (base 10) the least squares means and the lower and upper limits of the 97.5% CIs of the log transformed titres (base10) obtained from an Analysis of Variance

(ANOVA) with factors for vaccine lot and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)). Additionally, lot-to-lot GMT ratios will be computed for each pair of ABCWY lots. Ninety-seven point five percent (97.5%) CIs for the ratios of GMTs will be constructed by exponentiating the difference of the least square means of the log transformed titres and the lower and upper limits of the 97.5% CIs on the difference obtained from the ANOVA model above.

Lot-to-lot consistency criterion: The three ABCWY lots will be considered equivalent if for each of the 4 serogroups A, C, W and Y and each pair of vaccine lots, the two-sided 97.5% CI on the ratio of GMTs at 1 month after the last vaccination will be contained within the interval [0.5, 2.0].

If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.1.8. Immunological non-inferiority: MenABCWY vs. MenACWY

Analysis set: PPS restricted to subjects without previous ACWY vaccination will be the primary analysis population.

Statistical method: The percentage of subjects with 4-fold rise* in hSBA titres against MenACWY indicator strains A, C, W and Y and the corresponding exact two-sided 97.5% CIs based on Clopper-Pearson method will be calculated for the ABCWY (pooled lots) group and the ACWY group [Clopper, 1934]. The 97.5% CIs for the difference in percentages between ABCWY (pooled lots) and ACWY group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-Inferiority criterion: Non-inferiority of MenABCWY vaccine for the proportion of subjects with 4-fold rise will be demonstrated if the lower limit of the two-sided 97.5% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY (pooled) lots –ACWY) is above -10%.

* For the Men A, C, W, Y evaluation, the 4-fold rise is defined as:

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

Table 5 reads the LOD and LLOQ of MenACWY indicator strains used in the definition of 4-fold rise provided by the laboratory.

Table 5 LOD and LLOQ of MenACWY indicator strains

Strain	LOD	LLOQ
Men A (3125)	CCI [redacted]	
Men C (C11)		
Men W (240070)		
Men Y (860800)		

If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.1.9. Vaccine effectiveness (Test-based): MenABCWY

See Section 5.3.1.1. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the VE for MenABCWY will be evaluated at 95% CI.

5.3.1.10. Effectiveness non-inferiority: MenABCWY vs. rMenB+OMV NZ

Analysis set: PPS will be the primary analysis population.

Statistical method: The percentage of samples with bactericidal activity measured by enc-hSBA at 1:4 dilution and the corresponding exact two-sided 97.5% CIs based on Clopper-Pearson method will be calculated for the ABCWY (pooled lots) group and the MenB group comparator that will be selected (ref: the footnote of Figure 2). The 97.5% CIs for the difference in percentages between ABCWY (pooled lots) and selected MenB group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-Inferiority criterion: Non-inferiority of MenABCWY vaccine for the percentage of samples with bactericidal activity measured by enc-hSBA at 1:4 dilution will be demonstrated if the lower limit of the two-sided 97.5% CI for the difference between the 2 groups (ABCWY (pooled) lots – MenB) is above -5%.

If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.1.11. Effectiveness (Responder-based): MenABCWY

See Section 5.3.1.2. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the effectiveness (responder-based) for MenABCWY will be evaluated at 95% CI.

5.3.2. Additional considerations

Analyses of the primary effectiveness and immunogenicity objectives will be repeated by age group (10-17 years of age and 18-25 years of age), race, sex, region (US/ ex-US), and subjects with and without a previous MenACWY vaccination (primed and unprimed).

5.3.2.1. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

The SAS code to analyse the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) objective is specified below. Treatment, region, age category, previous ACWY vaccination, and strains will be modelled as fixed effect. To account for a possible over-dispersion, the DSCALE option in the model statement will be evaluated first. The DSCALE will be kept in the model only if the F-statistics for the DSCALE parameter is significant ($p<0.05$). The following SAS code will be used for the VE calculation:

```
ods trace on;
ods output GEEEmpPEst = genmod_stats
CONVERGENCESTATUS = converge ;

PROC GENMOD data=dataset descending;
class trtgrp strain region agecat previousACWY subject_id ;
model outcome = trtgrp strain region agecat previousACWY / dist= bin
link= log DSCALE;
repeated subject = subject_id / type= CS withinsubject= strain;
estimate 'MenB026-ACWY' trtgrp 1 0 0 0 0 -1/ alpha=0.025 exp;

/*trtgrp R is MenB0,2,6 and trtgrp W is ACWY*/

run;

ods output close;

data genmod_stats;
set genmod_stats;
where parm = 'trtgrp' and level1 = '1';
rr = exp(estimate);
ub = exp(uppercl);
ve = (1 - rr)*100 ;
ve_ll = (1 - ub) * 100 ;
if ve_ll > 65 then success = 1 ;
else success = 0 ;
run;
```

where outcome represents the Bernoulli distributed outcome without bactericidal activity at a 1:4 dilution (i.e. response is 1 if titre < 4, and 0 if titre ≥ 4), one month after the 3rd vaccination in MenB 0,2,6 and one month after the MenACWY vaccination for the ACWY arm, trtgrp indicates the vaccine groups, strain is the serogroup B strain variable, region is either US or ex-US, agecat is the age at enrolment (10-17 YoA or 18-25 YoA), and previousACWY is previous ACWY vaccination (y/n) at enrolment.

rr is the relative risk (RR), which is obtained from the estimated parameters from PROC GENMOD. Vaccine effectiveness (VE) is then derived as (1-rr)x100%.

ub represents the upper bound of the 97.5% CI of the relative risk. ve_ll is the lower bound of the 97.5% CI for VE, if the value is greater than 65%, then the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) objective is successful.

5.3.2.2. Effectiveness (Responder-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Not applicable

5.3.2.3. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 5.3.2.1, with the difference in the treatment arm:

```
PROC GENMOD data=dataset descending;
class trtgrp strain region agecat previousACWY subject_id ;
model outcome = trtgrp strain region agecat previousACWY / dist= bin
link= log DSCALE ;
repeated subject = subject_id / type= CS withinsubject= strain ;
estimate 'MenB06-ACWY' trtgrp 0 1 0 0 0 -1/ alpha=0.025 exp;

/*trtgrp S is MenB0,6 and trtgrp W is ACWY*/

run;
```

5.3.2.4. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

Not applicable

5.3.2.5. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 5.3.2.1, with the difference the outcome data for group R is from one month after the 2nd vaccination instead of one month after the 3rd vaccination.

5.3.2.6. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

Not applicable

5.3.2.7. Lot-to-lot consistency: MenABCWY - ACWY component

Not applicable

5.3.2.8. Immunological non-inferiority: MenABCWY vs. MenACWY

As a sensitivity analysis, a parametric model will be run. A generalized linear model with factors for vaccine group and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA)) will be ran, with the Binary distribution and link function is identity, and outcome is 4-fold rise. If the lower limit of the two-sided 97.5% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY (pooled) lots –ACWY) coming from the model is above -10%, also the sensitivity analysis has demonstrated non-inferiority. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

5.3.2.9. Vaccine effectiveness (Test-based): MenABCWY

See Section 5.3.2.1, with the difference in the estimate statement:

```
PROC GENMOD data=dataset descending;
class trtgrp strain region agecat previousACWY subject_id ;
model outcome = trtgrp strain region agecat previousACWY / dist= bin
link= log DSCALE ;
repeated subject = subject_id / type= CS withinsubject= strain ;
estimate ' MenABCWY-ACWY' trtgrp 0 0 1 1 1 -3/ alpha=0.025 exp
divisor=3;

/*trtgrp T, U, and V are the ABCWY-1, ABCWY-2, and ABCWY-3 lots and
trtgrp W is ACWY*/
run;
```

5.3.2.10. Effectiveness non-inferiority: MenABCWY vs. rMenB+OMV NZ

As a sensitivity analysis, a parametric model will be run. A generalized linear model with factors for vaccine group and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) will be ran, with the Binary distribution and link function is identity, and outcome is bactericidal activity measured by enc-hSBA at 1:4 dilution. If the lower limit of the two-sided 97.5% CI for the difference in percentage of samples with bactericidal activity measured by enc-hSBA at 1:4 dilution between the 2 groups (ABCWY (pooled) lots –MenB) coming from the model is above -5%, also the sensitivity analysis has demonstrated non-inferiority. If the co-primary effectiveness objectives for rMenB+OMV NZ are met (Sections 5.3.1.1 through 5.3.1.6), then the above will be evaluated at 95% CI.

In addition to the comparison of MenABCWY vs the selected MenB schedule per Section 5.3.1.10, MenABCWY will be compared to the other MenB schedule/schedules, whichever is applicable in the same way as described in Section 5.3.1.10. If MenB 0,2 schedule is selected as comparator, in addition MenABCWY will be compared to Menb 0,6 and MenB 0,2,6 schedule. If MenB 0,6 schedule is selected as comparator, in addition MenABCWY will be compared to MenB 0,2,6 schedule. No success criterion is defined for these group comparisons.

5.3.2.11. Effectiveness (Responder-based): MenABCWY

Not applicable

5.4. Secondary effectiveness and immunogenicity

5.4.1. Analysis of secondary effectiveness and immunogenicity planned in the protocol

5.4.1.1. Immunological non-inferiority: MenABCWY vs. rMenB+OMV NZ

Analysis set: PPS will be the primary analysis population.

Statistical method: The percentages of subjects with 4-fold rise** in hSBA titres against N. meningitidis serogroup B indicator strains (M14459, 96217, M07-0241084* and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively) at 1 month after the last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) and 1 month after the 3-dose vaccination series (Day 211, Month 7) in MenB_0_2_6 group or 2-dose vaccination series (Day 211, Month 7) in MenB_0_6 group or 2-dose vaccination series (Day 91, Month 3) in MenB_0_2_6 group and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated [Clopper, 1934]. The 95% CIs for the difference in percentages between ABCWY group (pooled lots) and MenB_0_2_6 group and MenB_0_6 group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-inferiority criterion: Non-inferiority of MenABCWY vaccine for the proportion of subjects with 4-fold rise will be demonstrated if the lower limit of the 2-sided 95% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY group (pooled lots) –selected MenB group) is above -10%.

* The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented either in a protocol amendment or in the clinical report.

** For the MenB evaluation, the 4-fold rise per each indicator strain is defined as:

- a post-vaccination‡ hSBA titre ≥4 times the LOD for subjects with a pre-vaccination hSBA titre <LOD
- a post-vaccination‡ hSBA titre ≥4 times the LLOQ for subjects with a pre-vaccination hSBA titre ≥LOD and <LLOQ, and
- a post-vaccination‡ hSBA titre ≥4 times the pre-vaccination hSBA titre for subjects with a pre-vaccination hSBA titre ≥LLOQ

‡ = post-2nd vaccination for 0,6 and 0,2 schedule and post-3rd vaccination for 0,2,6 schedule).

Table 6 reads the LOD and LLOQ of hSBA titres against N. meningitidis serogroup B indicator strains used in the definition of 4-fold rise provided by the laboratory.

Table 6 LOD and LLOQ of hSBA titres against N. meningitidis serogroup B indicator strains

Strain	LOD	LLOQ
NZ98-254	CCI [redacted]	
96217		
M14459		
M13520		

5.4.1.2. Effectiveness by each of the endemic US N. meningitidis serogroup B strains

Analysis set: FAS will be the primary analysis population. The ABCWY (pooled lots) group and the MenB group comparator that will be selected (ref: the footnote of Figure 2) will be used for the purpose of this analysis.

Statistical method: The VE per strain will be calculated as described in Section 5.3.1.1, using a generalised linear model with vaccine group, and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) as independent variables, and alpha=0.05 leading to 95% CI. In case for a strain 100% response will be observed in both vaccine groups, VE against these strain will be assessed by calculating 95% CI for relative risk from raw proportions, and VE=1-RR.

5.4.1.3. Distribution of percentages of serogroup B invasive disease strains killed

Analysis set: FAS will be the primary analysis population. The ABCWY (pooled lots) group and the MenB group comparator that will be selected (ref: the footnote of Figure 2) will be used for the purpose of this analysis.

Statistical method: Summary statistics of the percentage of serogroup B invasive disease strains killed within a subject using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series of rMenB+OMV NZ and MenABCWY vaccines.

Summary statistics and 95% CI for the mean percentage will be presented, as well as a Figure of the cumulative distribution function.

5.4.1.4. Immune response of MenABCWY, rMenB+OMV NZ and MenACWY

Analysis set: The analysis will be based on the FAS.

Statistical method: The hSBA titres at each time point for all groups (ABCWY group (pooled lots), MenB_0_2_6 and MenB_0_6 groups) will be logarithmically transformed (base10) to fulfil the normal distribution assumption. For each N. meningitidis serogroup A, C, W and Y and each B indicator strain (M14459, 96217, M07-0241084* and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively), the GMTs and GMRs (post-vaccination/baseline) will be obtained from an Analysis of Variance (ANOVA) with factors for vaccine group, region (US/ex-US), age category (10-17 YoA/18-25 YoA), and previous MenACWY vaccination (y/n), and then exponentiating the log-transformed means and their 95% CIs. The ratio of GMTs and GMRs between two groups and the corresponding CI will be estimated additionally.

The total IgG (as measured by ECL) against serogroups A, C, W and Y at baseline (Day 1, Month 0) and

- at 1 month after the first (Day 31, Month 1) and the last vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and
- at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1),

will be analyzed in a comparable way as described above for hSBA titres. Since total IgG is measured as concentration instead of titer, the resulting geometric mean of the concentrations is abbreviated as GMC.

For each N. meningitidis A, C, W and Y and for each (individual response) and all (composite response serogroup B indicator strain (M14459, M07-0241084*, 96217and NZ98/254) the percentages of subjects with hSBA titres ≥LLOQ and of subjects with 4-fold rise and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated for each study group at each timepoint not previously analyzed. Ninety-five percent (95%) CIs for the difference in percentages between ABCWY (pooled lots) on the one hand and MenB_0_2_6, MenB_0_6, and ACWY groups, respectively, on the other hand, will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

* The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented either in a protocol amendment or in the clinical report.

5.4.2. Additional considerations

5.4.2.1. Immunological non-inferiority: MenABCWY vs. rMenB+OMV NZ

As a sensitivity analysis, a parametric model will be run. A generalized linear model with factors for vaccine group and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) will be ran, with the

Binary distribution and link function is identity, and outcome is 4-fold rise. If the lower limit of the two-sided 95% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY (pooled) lots –MenB) coming from the model is above -10%, also the sensitivity analysis has demonstrated non-inferiority.

5.4.2.2. Effectiveness by each of the endemic US N. meningitidis serogroup B strains

The SAS code to analyse the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) by strain is specified below. Treatment, and randomization factors (i.e. region (US/ex-US), age category (10-17 YoA/18-25 YoA), previous MenACWY vaccination (y/n)) will be modelled as fixed effect. To account for a possible over-dispersion, the DSCALE option in the model statement will be evaluated first. The DSCALE will be kept in the model only if the F-statistics for the DSCALE parameter is significant ($p<0.05$). The following SAS code will be used for the VE calculation:

```
ods trace on;
ods output  GEEEmpPEst = genmod_stats
CONVERGENCESTATUS = converge ;

PROC GENMOD data=dataset descending;
class trtgrp region agecat previousACWY;
by strain ;
model outcome = trtgrp region agecat previousACWY / dist= bin link= log
DSCALE alpha=0.05;
estimate 'MenB026-ACWY' trtgrp 1 0 0 0 0 -1/ alpha= 0.05 exp;

/*trtgrp R is MenB0,2,6 and trtgrp W is ACWY*/

run;

ods output close;

data genmod_stats;
set genmod_stats;
by strain ;
where parm = 'trtgrp' and level1 = '1';
rr = exp(estimate);
ub = exp(uppercl);
ve = (1 - rr)*100 ;
ve_ll = (1 - ub) * 100 ;
if ve_ll > 65 then success = 1 ;
else success = 0 ;
run;
```

where outcome represents the Bernoulli distributed outcome without bactericidal activity at a 1:4 dilution (i.e. response is 1 if titre < 4, and 0 if titre ≥ 4), one month after the 3rd vaccination in MenB0,2,6 and one month after the MenACWY vaccination for the ACWY arm, trtgrp indicates the vaccine groups, strain is the serogroup B strain variable, region is either US or ex-US, agecat is the age at enrolment (10-17 YoA or 18-25 YoA), and previousACWY is previous ACWY vaccination (y/n) at enrolment.

rr is the relative risk (RR), which is obtained from the estimated parameters from PROC GENMOD. Vaccine effectiveness (VE) is then derived as (1-rr)x100%.

ub represents the upper bound of the 95% CI of the relative risk. ve_ll is the lower bound of the 95% CI for VE, if the value is greater than 65%, then the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) objective is successful.

In summary in case of convergence issue the following hierarchical decision tree will be applied

- Binary model including region, agecat, and previousACWY

- Binary model, excluding region, agecat, and previousACWY

- Cochran-Mantel-Haenszel (CMH) method (if strain has 100% killed or 0% killed for ANY treatment)

- VE set to 0% (if strain has 100% killed for both treatment)

5.4.2.3. Distribution of percentages of serogroup B invasive disease strains killed

Not applicable

5.4.2.4. Immune response of MenABCWY, rMenB+OMV NZ and MenACWY

Not applicable

5.5. Safety and reactogenicity

5.5.1. Analysis of safety and reactogenicity planned in the protocol

Distribution of subjects by vaccinations will be summarised by vaccine group for the Enrolled Set. In case of vaccination error, subjects will be analyzed “as treated” (according to the vaccine the subject received).

Analysis sets: Solicited Safety Set (solicited local and systemic adverse events and other solicited adverse events), Unsolicited Safety Set (unsolicited adverse events), and Overall Safety Set.

Endpoint	Statistical Analysis Methods
Primary	**Endpoints description**: The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) adverse events during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. All solicited adverse events will be summarised according to defined severity grading scales, see protocol section 12.5.9.3. Frequencies and percentages of subjects experiencing each adverse event will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic adverse event overall and at each time point will also be presented. Post-vaccination solicited adverse events reported from Day 1 to Day 7 will be summarised for the intervals Day 1-3, Day 4-7, and Day 1-7 by maximal severity and by vaccine group, excluding the 30-minute measurement, which will be summarised separately. The severity of solicited local adverse events, including redness (erythema) at injection site, swelling of skin at injection site, and hardness of skin at injection site will be summarised according to categories based on linear measurement: None (1 to 24mm); Mild (25 to 50mm); Moderate (51 to 100mm); Severe (>100mm). Injection site tenderness and systemic reactions (except fever) occurring up to 7 days after each vaccination at Day 1, Day 61 and Day 181 will be summarised according to "mild", "moderate" or "severe". Each solicited local and systemic adverse event will also be further summarised as "none" versus "any" (for fever the latter will be ≥38.0 °C). Use of antipyretics and analgesics will be summarised by frequency by type of use (prophylactic versus treatment) and percentage of subjects reporting use. Body temperature will be summarised 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 temperatures ≥ 38.0 °C and temperatures ≥ 40.0 °C will also be presented.
	Endpoints description: The frequencies and percentages of subjects with any unsolicited ***AEs*** (including all SAEs), ***AEs*** leading to withdrawal and medically attended ***AEs*** during the 7 and the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. The frequencies and percentages of subjects with SAEs, ***AEs*** leading to withdrawal***, AESIs*** and medically attended ***AEs*** throughout the study period. This analysis applies to all adverse events occurring during the study, judged either as possibly related, or not related to vaccination by the investigator, recorded in AE CRF, with a start date on or after the date of first vaccination. AE starting prior to the first vaccination will only be listed. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class. All reported adverse events, as well as adverse events judged by the investigator as possibly related to study vaccine, will be summarised 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 adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted. Separate summaries will be produced for the following categories: • Serious adverse events. • Adverse events that are possibly related to vaccine. • Adverse events of special interest. • Adverse event leading to withdrawal. • Adverse events leading to a medically attended visit. Data listings of all adverse events will be provided by subject. In addition, adverse events in the categories above will be provided as listed data. Local and systemic AEs will be analyzed by point estimates with associated 95% CIs [Clopper, 1934].

5.5.2. Additional considerations

For analyses of the safety and reactogenicity endpoints, subjects will be analyzed "as treated" according to the actual vaccination a subject received.

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

Analyses of safety objectives will be repeated by age group (10-17 years of age and 18-25 years of age), race, sex, region (US/ ex-US), and with and without a previous MenACWY vaccination (primed and unprimed).

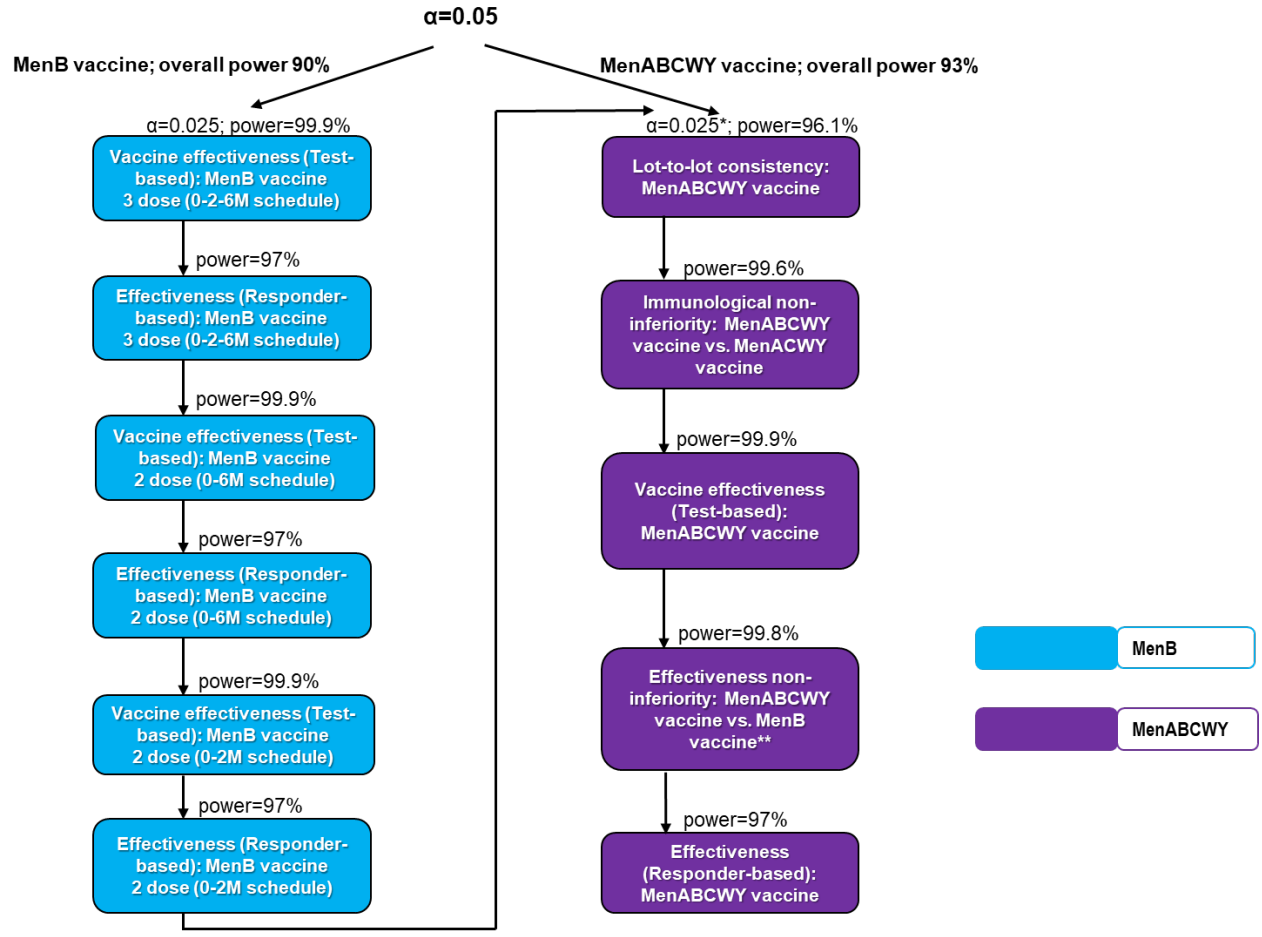
A Table and Listing of COVID-19 AE cases will be provided.

6. ANALYSIS INTERPRETATION

Multiple objectives and endpoints require type I error control. Full alpha (0.05) is split equally (alpha=0.025) between rMenB+OMV NZ objectives and MenABCWY objectives. Furthermore, within rMenB+OMV NZ, as well as within MenABCWY, objectives are tested hierarchically. If the first null hypothesis is rejected, then the testing will continue with the second hypothesis at same alpha. Same for 3rd, 4th, and so forth. Whenever a null hypothesis is not rejected, then the testing will stop.

As the comparator for MenABCWY non inferiority objective for the B component will be the selected schedule of rMenB+OMV NZ as determined in this study, the objectives of rMenB+OMV NZ will be analysed first. Additionally, if all null hypotheses related to rMenB+OMV NZ objectives will be rejected, the alpha (alpha=0.025) will be propagated to the MenABCWY part, and hypotheses related to MenABCWY objectives will be tested at full alpha (alpha=0.05). See Figure 2 for an explanation of the hierarchical testing (top to bottom, the order indicated by the arrows).

Figure 2 Hierarchical testing of hypothesis



* Alpha split equally between rMenB+OMV NZ and MenABCWY vaccine objectives.
If all rMenB+OMV NZ objectives achieved, MenABCWY vaccine objectives will be tested at full alpha.
** If all objectives of rMenB+OMV NZ are met, the comparator will be the 0,2-months schedule. If the 0,2-months objective is not met, and the 0,6-months is met, then the 0,6-months schedule will be the comparator. If the 0,6-months is also not met, then the 0,2,6-months schedule will be the comparator.

Refer to Glossary of terms for definitions of test-based and responder-based vaccine effectiveness.

7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

The final study report will contain at least the final analyses of all primary and secondary endpoints.

7.2. Statistical considerations for interim analyses

No interim analysis is planned for this study

8. CHANGES FROM PLANNED ANALYSES

Not applicable

9. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

The following sections describe additional derivation rules and statistical methods which are not presented in section 10.1.

9.1. Data derivation

Not applicable

9.2. Statistical Method

Not applicable

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

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

10.1.1. Attributing events to vaccine doses

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

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

10.1.2. Handling of missing data

10.1.2.1. Dates

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

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

The following exceptions apply:

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

year. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that year.

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

10.1.2.2. Laboratory data

Missing laboratory results (including immunological data) will not be replaced.

10.1.2.3. Daily recording of solicited adverse events

10.1.2.3.1. Studies with electronic diaries

For studies using electronic diaries for the collection of solicited adverse events, a solicited adverse events will be considered present only when a daily recording of grade 1 or more is present.

10.1.2.4. Unsolicited adverse events

Unsolicited adverse event summaries are including serious adverse events unless specified otherwise.

Missing severity, relationship with study vaccine, and outcome of unsolicited adverse events will not be replaced and will appear as 'UNKNOWN' in all statistical output.

10.1.3. Data derivation

10.1.3.1. Age at vaccination in days

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

Age = date of vaccination minus date of birth

10.1.3.2. Age at vaccination in months

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

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

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

10.1.3.3. Age at vaccination in years

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

DOB = 10SEP1983, Date of vaccination = 09SEP2018 -> Age = 34 years

DOB = 10SEP1983, Date of vaccination = 10SEP2018 -> Age = 35 years

10.1.3.4. Weight

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

Weight in kilograms = Weight in pounds / 2.2

10.1.3.5. Height

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

Height in centimeters = Height in inches x 2.54

10.1.3.6. Body mass index (BMI)

BMI will be calculated as follows:

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

10.1.3.7. Temperature

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

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

10.1.3.8. Numerical serology results

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

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

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

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

10.1.3.10. Onset day

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

10.1.3.11. Duration of events

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

10.1.3.12. Counting rules for combining solicited and unsolicited adverse events

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

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

10.1.3.13. Counting rules for occurrences of solicited adverse events

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

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with:

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

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

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

10.1.4.2. Differences in percentages

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

10.1.4.3. Demographic/baseline characteristics statistics

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

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

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

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

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

10.1.4.4. Serological summary statistics

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

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

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

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

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

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

10.1.5.2. Standardized asymptotic confidence intervals around differences in proportions

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

10.2. TFL TOC

The Tables Figures and Listings (TFL) Table of Contents (TOC) which itemizes the planned list of TFL and their associated lay-out is developed as a separate document.

10.3. Glossary of terms

End of Study (EoS) **(Synonym of End of Trial)**	For studies with collection of human biological samples and/or imaging data, the EoS is defined as Last subject last visit (T10). or Last testing results released of samples collected at Visit 6* * In this case EoS must be achieved no later than 8 months after LSLV.
Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.
Responder-based vaccine effectiveness:	The enc-hSBA methodology involves testing the serum samples from each individual subject against a subset of around 35 strains randomly chosen from the overall panel of 110 meningococcus B US strains. Responder-based vaccine effectiveness is assessed based on the percentage of subjects considered responders, i.e., subjects whose serum kills the majority (≥70% in this study) of the tested strains following vaccination.
Test-based vaccine effectiveness:	The enc-hSBA methodology involves testing the serum samples from each individual subject against a subset of around 35 strains randomly chosen from the overall panel of 110 meningococcus B US strains. Test-based vaccine effectiveness is assessed based on the overall percent of individual positive tests following vaccination and represents the reduction in risk compared to the placebo.

11. REFERENCES

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Clopper CJ, Pearson E. The Use of Confidence or Fiducial Limits Illustrated in the case of the Binomial. *Biometrika.* 1934;26:404-13.

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

GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A phase III, randomized, controlled, observer-blind study to demonstrate effectiveness, immunogenicity and safety of GSK's meningococcal Group B and combined ABCWY vaccines when administered to healthy adolescents and young adults.
eTrack study number and Abbreviated Title	205416 [MENB REC 2ND GEN-038 (V72_72)]
Scope:	All data pertaining to the above study
Date of Statistical Analysis Plan	Final: 15 June 2020

APP 9000058193 Statistical Analysis Plan Template V4 (Effective date: 3June2019)

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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
Eli Type	Internal database code for type of elimination code
ELISA	Enzyme-linked immunosorbent assay
EOS	End of Study
ES	Exposed Set
FAS	Full Analysis Set
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titre
GSK	GlaxoSmithKline
LL	Lower Limit of the confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
PCD	Primary completion Date
PPS	Per-Protocol Set
RR	Relative Risk
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
TFL	Tables Figures and Listings
TOC	Table of Contents

1. DOCUMENT HISTORY

Date	Description	Protocol Version
25 JUL 2019	First version	Amendment 1: 23 MAY 2019
15 JUN 2020	Amendment 1	Amendment 2: 18 MAR 2020

2. OBJECTIVES/ENDPOINTS

Table 1 Study objectives and endpoints

Objectives	Endpoints
Primary	
Vaccine effectiveness (Test-based): rMenB+OMV NZ To demonstrate the effectiveness of the rMenB+OMV NZ vaccine against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity using enc-hSBA at 1 month after the 3-dose (0,2,6-months) and 2-dose (0,6-months; 0,2-months) vaccination series when compared to 1 month after the MenACWY vaccination. *Criterion* *Lower limit (LL) of the two-sided 97.5% confidence interval (CI) for vaccine effectiveness is above 65% against a randomly selected strain panel between the:* • *MenB_0_2_6 and ACWY groups (for 0,2,6-months schedule)* • *MenB_0_6 and ACWY groups (for 0,6-months schedule),* • *MenB_0_2_6 and ACWY groups (for 0,2-months schedule)*	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at 1 month after the: • 3-dose vaccination series in MenB_0_2_6 group (Day 211, Month 7) • 2-dose vaccination series in MenB_0_6 group (Day 211, Month 7), and • 2-dose vaccination series in MenB_0_2_6 group (Day 91, Month 3) • 1 month after the MenACWY vaccination in ACWY group (Day 31, Month 1).
Effectiveness (Responder-based): rMenB+OMV NZ To demonstrate the effectiveness of the rMenB+OMV NZ vaccine by assessing the percentages of subjects whose sera kill ≥70% of strains tested using enc-hSBA at 1 month after the 3-dose (0,2,6-months) and 2-dose (0,6-months; 0,2-months) vaccination series of the rMenB+OMV NZ. *Criterion:* *LL of the two-sided 97.5% CI for the percentages of subjects whose sera kill ≥70% of strains is above 65%, tested for:* • *MenB_0_2_6 group (for 0,2,6-months schedule)* • *MenB_0_6 group (for 0,6-months schedule),* • *MenB_0_2_6 group (for 0,2-months schedule)*	The percentages of subjects whose sera kill ≥70% of the strains tested using enc-hSBA, at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group), • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group)
The 3 vaccine schedules will be tested for both, test-based and responder-based, in a hierarchical way (starting from 0-2-6, to 0-6 and 0-2). Refer to Protocol Section 10.1 for details on continuing the evaluation.	

Objectives	Endpoints
Lot-to-lot consistency: MenABCWY vaccine To demonstrate lot-to-lot consistency of the immune responses of 3 lots of the MenACWY component of the MenABCWY vaccine, as measured by hSBA GMTs directed against serogroups A, C, W and Y at 1 month after last vaccination (0,6-months). *Criterion:* *The two-sided 97.5% CIs^ for the ratio of hSBA GMTs of antibodies against serogroups A, C, W and Y are within the [0.5;2.0] equivalence interval for each pair of lots.*	GMTs directed against serogroups A, C, W and Y for each lot (ABCWY-1 group, ABCWY-2 group, ABCWY-3 group) at 1 month after the last vaccination (Day 211, Month 7)
Immunological non-inferiority: MenABCWY vaccine vs. MenACWY vaccine To demonstrate the immunological non-inferiority of the MenABCWY vaccine compared to the MenACWY vaccine as measured by the percentages of subjects achieving a 4-fold rise in hSBA titres against *N. meningitidis* serogroups A, C, W and Y at 1 month after the last MenABCWY vaccination (0,6-months) and 1 month after the MenACWY vaccination. *Criterion:* *LL of the 2-sided 97.5% CI^ for the group difference in percentages of subjects achieving a 4-fold rise* in hSBA titres is above -10%.*	The percentages of subjects with 4-fold rise* in hSBA titres against *N. meningitidis* serogroups A, C, W and Y at 1 month after the: • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • 1 month after the MenACWY vaccination for the ACWY group (Day 31, Month 1) relative to baseline (Day 1, Month 0).
Vaccine effectiveness (Test-based): MenABCWY vaccine To demonstrate the effectiveness of the MenABCWY vaccine against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains as measured by enc-hSBA at 1 month after the last MenABCWY vaccination (0,6-months) when compared to 1 month after the MenACWY vaccination. *Criterion:* *LL of the two-sided 97.5% CI^ for vaccine effectiveness is above 65% against a randomly selected strain panel between the ABCWY group (pooled lots) and the ACWY group.*	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at 1 month after the: • last vaccination for the ABCWY group (pooled) (Day 211, Month 7), and • 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1).
Effectiveness non-inferiority: MenABCWY vaccine vs. rMenB+OMV NZ vaccine To demonstrate the non-inferiority of the effectiveness of the MenABCWY vaccine (0,6-months schedule) compared to the rMenB+OMV NZ vaccine (0,2,6-months or 0,6-months or 0,2-months) † in terms of percentage of samples with bactericidal serum activity using enc-hSBA against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains. *Criterion:* *LL of the two-sided 97.5% CI^ for the difference in percentages of samples with bactericidal serum activity using enc-hSBA against a randomly selected panel of*	The percentages of samples with bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains at 1 month after the: • last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • 3-dose vaccination series of rMenB+OMV vaccine (Day 211, Month 7 in MenB_0_2_6 group) or 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) or 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group) †

Objectives	Endpoints
endemic US N. meningitidis serogroup B invasive disease strains is above -5% at 1 month after: • *the last vaccination in ABCWY group (pooled lots) (for 0,6 months schedule), and* • *The last vaccination in MenB_0_2_6 group (for 0,2,6-months schedule) or the last vaccination in MenB_0_6 group (for 0,6-months schedule) or the second vaccination in MenB_0_2_6 group (for 0,2-months schedule*	
Effectiveness (Responder-based): MenABCWY vaccine To demonstrate the effectiveness of MenABCWY vaccine by assessing the percentages of subjects whose sera kill ≥70% of strains tested using enc-hSBA at 1 month after the last vaccination of MenABCWY (0,6-months). *Criterion:* *LL of the two-sided 97.5% CI^ for the percentages of subjects whose sera kill ≥70% of strains tested for MenABCWY is above 65%.*	The percentages of subjects whose sera kill ≥70% of the strains tested using enc-hSBA, at 1 month after the last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7).
Safety To evaluate the safety and reactogenicity of the MenB, MenABCWY, and the MenACWY vaccines	• The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [body temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) adverse events (AEs) during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. • The frequencies and percentages of subjects with any unsolicited AEs (including all SAEs, AEs leading to withdrawal, AESIs and medically attended AEs) during the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. • The percentages of subjects with SAEs, AEs leading to withdrawal, AESIs and medically attended AEs throughout the study period [Month 0 to Month 18].
Secondary	
To demonstrate the immunological non-inferiority of the MenABCWY vaccine compared to the rMenB+OMV NZ vaccine as measured by the percentages of subjects achieving a 4-fold rise in hSBA titres against *N. meningitidis* serogroup B indicator strains at 1 month after the last MenABCWY vaccination (0,6-months schedule) and 1 month after the rMenB+OMV NZ vaccination (0,2,6-months or 0,6-months or 0,2-months) † *Criterion:* *Non-inferiority will be demonstrated if the LL of the 2-sided 95% CI for the group difference in percentage of*	The percentages of subjects with 4-fold rise** in hSBA titres against *N. meningitidis* serogroup B indicator strains at 1 month after the: • last MenABCWY vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • 3-dose vaccination series of rMenB+OMV vaccine(Day 211, Month 7 in MenB_0_2_6 group) or 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) or 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group) † relative to baseline (Day 1, Month 0).

Objectives	Endpoints
*subjects achieving a 4-fold rise** in hSBA titres against N. meningitidis serogroup B indicator strains is above -10%.*	
To assess the effectiveness of the rMenB+OMV NZ and MenABCWY vaccines against each of the randomly selected endemic US *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series when compared to 1 month after the MenACWY vaccination.	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group) • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • MenACWY vaccination (Day 31, Month 1 in ACWY group).
To describe the distribution of subjects by percentages of serogroup B invasive disease strains killed using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series of rMenB+OMV NZ and MenABCWY vaccines.	The percentages of serogroup B invasive disease strains killed using enc-hSBA in each subject at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7)
To assess the immune response to the rMenB+OMV NZ (0,2,6-months, 0,6-months and 0,2-months) and MenABCWY (0,6-months) vaccines against *N. meningitidis* serogroup B indicator strains at pre-vaccination (Day 1, Month 0) and at 1 month after the last MenABCWY vaccination and at 1 month after the second and third vaccination of rMenB+OMV NZ.	The immune response to the rMenB+OMV NZ and ABCWY vaccines will be evaluated by measuring bactericidal activity against *N. meningitidis* serogroup B indicator strains as following: *1. The percentages of subjects with hSBA titres ≥ lower limit of quantitation (LLOQ) for each (individual response) and all (composite response) serogroup B indicator strains at baseline (Day 1, Month 0) and at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *2. The percentages of subjects with 4-fold rise** in hSBA titres at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 90, Month 3 in MenB_0_2_6 group), and

Objectives	Endpoints
	• last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *relative to baseline (Day 1, Month 0).* *3. hSBA GMTs at baseline (Day 1, Month 0) and at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *4. hSBA GMRs at 1 month after the:* • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *relative to the baseline (Day 1, Month 0).*
To assess the immune response to MenABCWY (0,6-months schedule) and MenACWY (single dose) vaccines against *N. meningitidis* serogroups A, C, W and Y, at pre-vaccination (Day 1, Month 0) and at 1 month after the first and the last MenABCWY vaccination and 1 month after the MenACWY vaccination.	*1. The percentage of subjects with hSBA titres ≥ LLOQ for serogroups A, C, W and Y at baseline (Day 1, Month 0) and:* • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1). *2. The percentage of subjects with 4-fold rise* in hSBA titres at 1 month after the:* • first vaccination (Day 31, Month 1) for the ABCWY group (pooled lots) compared to the MenACWY vaccination in the ACWY group (Day 31, Month 1) *relative to baseline (Day 1, Month 0).* *3. hSBA GMTs against N. meningitidis serogroups A, C, W and Y* at baseline (Day 1, Month 0) and: • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1). *4.hSBA GMRs against N. meningitidis serogroups A, C, W and Y at:* • 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots) as compared to baseline (Day 1, Month 0), and

Objectives	Endpoints
	• 1 month after the single MenACWY vaccination in the ACWY group (Day 31, Month 1) as compared to baseline (Day 1, Month 0). *5.The total IgG as measured by ELISA GMCs against serogroups A, C, W and Y* at baseline (Day 1, Month 0) and*:* • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1).

Abbreviations: ELISA = enzyme-linked immunosorbent assay; Enc-hSBA = endogenous complement human serum bactericidal assay; GMC = geometric mean concentrations; GMT = geometric mean titre; GMR = geometric mean ratio; CI = confidence interval; hSBA = human serum bactericidal assay; LOD: limit of detection; LLOQ = lower limit of quantitation; LL = lower limit; AE = Adverse event; SAE = Serious adverse event; AESI = Adverse event of special interest

N.meningitidis serogroup B indicator strains = M14459, 96217, M07-0241084 and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively. The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented either in a protocol amendment or in the clinical report.

Refer to Protocol Section 10 for details on evaluation of objectives and sample size justification. Refer to Glossary of terms for definitions of test-based and responder-based effectiveness

^ If the co-primary effectiveness objectives for rMenB+OMV NZ are met, then all objectives for MenABCWY will be evaluated at 95% CI. Refer to Protocol Section 10.1 for details

† If all objectives of rMenB+OMV NZ are met, the comparator will be the 0,2-months schedule. If the 0,2-months objective is not met, and the 0,6-months is met, then the 0,6-months schedule will be the comparator. If the 0,6-months is also not met, then the 0,2,6-months schedule will be the comparator.

*For the Men A, C, W, Y evaluation, the 4-fold rise is defined as:

- a post-vaccination hSBA titre ≥16 for subjects with a pre-vaccination hSBA titre <4
- a post-vaccination hSBA titre ≥4 times the LLOQ for subjects with a pre-vaccination hSBA titre ≥LOD but <LLOQ, and
- a post-vaccination hSBA titre ≥4 times the pre-vaccination titre for subjects with a pre-vaccination hSBA titre ≥LLOQ.

**For the MenB evaluation, the 4-fold rise per each indicator strain is defined as:

- a post-vaccination‡ hSBA titre ≥16 for subjects with a pre-vaccination hSBA titre <4
- a post-vaccination‡ hSBA titre ≥4 times the LLOQ for subjects with a pre-vaccination hSBA titre ≥LOD and <LLOQ, and
- a post-vaccination‡ hSBA titre ≥4 times the pre-vaccination hSBA titre for subjects with a pre-vaccination hsBA titre ≥ LLOQ

‡ = post-2nd vaccination for 0,6 and 0,2 schedule and post-3rd vaccination for 0,2,6 schedule.

3. STUDY DESIGN

3.1. Scientific rationale for study design

As the rMenB+OMV NZ licensure in the US was issued through accelerated approval, the FDA has requested to demonstrate the effectiveness of the vaccine against an extended panel of serogroup B meningococcal strains (MenB) as a post-marketing commitment in US adolescents and young adults, thus confirming that the vaccine can protect against diverse meningococcal B strains prevalent in the United States.

The availability of a pentavalent meningococcal vaccine in a single administration would however reduce the number of injections and could increase coverage for meningococcal disease caused by *N. meningitidis* serogroups A, B, C, W, and Y worldwide. GSK's investigational MenABCWY combination vaccine is intended to protect against 5 of the most prevalent serogroups of *Neisseria meningitidis* (A, B, C, W, Y) in humans.

Hence, along with the licensed MenB vaccine (*Bexsero*), this Phase III study will also assess the safety, effectiveness, and immunogenicity of the investigational MenABCWY vaccine.

Rationale for effectiveness assessment

As mentioned above, one of the primary purposes of this study is to evaluate the effectiveness of 2 or 3 doses of rMenB+OMV NZ and of 2 doses of the MenABCWY vaccines in healthy adolescents and young adults by measuring the bactericidal activity against 110 endemic US *N. meningitidis* serogroup B strains using an endogenous complement human Serum Bactericidal Assay (enc-hSBA). Sera from the ACWY group receiving the MenACWY vaccine will also be tested against serogroup B meningococcal strains by enc-hSBA as a control for test-based effectiveness assessment. The overall vaccine effectiveness (VE) against all 110 strains combined will be computed by means of a generalised linear model. For additional details see statistical analysis section of the Clinical Study Protocol (Protocol Section 10).

Rationale for lot-to-lot consistency assessment

MenABCWY is a reconstituted vaccine with the lyophilised 'ACWY component' and liquid rMenB+OMV NZ. The MenB component has the same formulation as the commercial *Bexsero*. To demonstrate that the lots of the investigational MenABCWY vaccine are adequately representative of the formulation intended for marketing, equivalence will be assessed for 3 different lots of the ACWY component of the ABCWY vaccine.

Rationale for non-inferiority assessment of MenABCWY vs MenACWY and rMenB+OMV NZ

The study aims to also demonstrate that the investigational combination MenABCWY vaccine is not inferior to a licensed MenACWY vaccine (*Menveo*) and a licensed MenB vaccine (*Bexsero*) which are part of the current standards of care in the US for prevention of invasive disease caused by *N. meningitidis* serogroups A, C, W, Y and by *N. meningitidis* serogroup B, respectively.

Rationale for blood volume collected:

In order to provide the necessary serum volume for the bactericidal assays (enc-hSBA and/ or hSBA(s)), 25 mL whole blood will be collected at Visit 2, Visit 4 and Visit 6. At pre-vaccination (Visit 1), 20 mL whole blood will be collected to provide the necessary serum volume for the hSBA.

Blood samples are taken from all subjects irrespective of the testing status in order to maintain the study blind. Refer to Protocol Section 8.4.2.1 for further details.

Rationale for the selected vaccination schedules

rMenB+OMV NZ: This study aims at demonstrating the VE of the rMenB+OMV NZ vaccine administered as 2-dose vaccine, either with a shorter interval (0,2-months) or a prolonged interval (0,6-months) between doses. A 3-dose schedule has been also added to better characterise the VE.

Note: The rMenB+OMV NZ in the ACWY group is administered in a 0,1-months schedule. This interval is within the recommendations in the summary of product characteristics of *Bexsero* and helps in maintaining the blind. No objectives are associated with this schedule of rMenB+OMV NZ.

MenABCWY: A number of different vaccine formulations were evaluated in MenABCWY Phase I and II clinical studies. The formulation with the same active ingredient composition as the rMenB+OMV NZ (*Bexsero*) and MenACWY (*Menveo*) vaccines was chosen as the final formulation of the investigational MenABCWY vaccine. Two doses administered 6 months apart (0,6-months) is considered the optimal dosing schedule, based on serogroup B immunogenicity results from MenABCWY Phase II clinical studies.

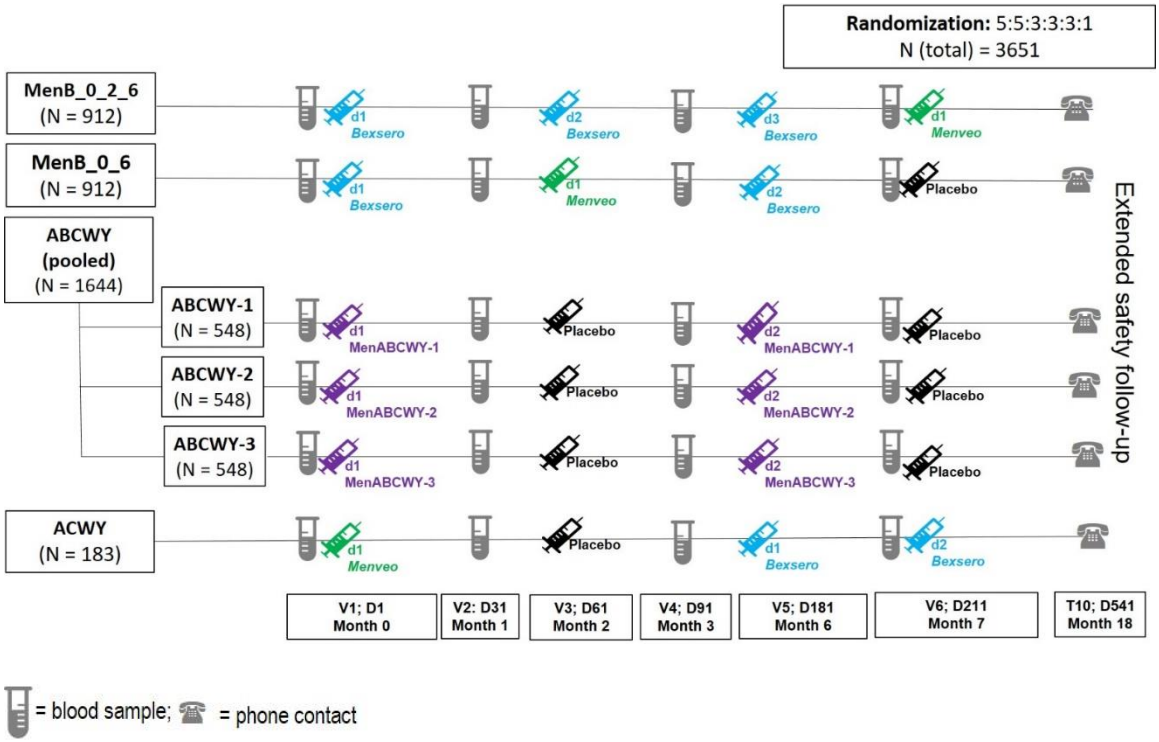
MenACWY: As a comparator for serogroup A, C, W, and Y vaccine effectiveness and immune responses, a single dose of MenACWY vaccine is administered to subjects in the ACWY group. To conform with the standard of care (also in alignment with current ACIP routine immunisation recommendations in US), subjects in the MenB_0_2_6 and MenB_0_6 groups will also receive a dose of MenACWY at Day 211 and Day 61, respectively.

3.1.1. Rationale for the use of placebo

For this study, a placebo (saline solution) will be administered as presented in Figure 1. A placebo is the only available option to minimize possible introduction of reporting bias in collecting information about AEs and to ensure the same number of vaccinations are administered to subjects assigned to either of the six study groups.

3.2. Overall design

Figure 1 Study design overview



N = number of subjects; d = dose; V = visit; D = day; T=Telephone call
Refer to Protocol Table 3 for details on all visits
Note: Home visits may be performed only by sites authorised (as per local regulations and sponsor agreement), with approved site level standard operating procedures (SOP) provided that the compliance with protocol procedures are ensured.

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the schedule of activities (Protocol Section 2), are essential and required for study conduct.

- Type of study: self-contained

- Experimental design: This is a phase III, randomised, controlled, observer-blind, multi-center study to evaluate effectiveness, immunogenicity and safety of rMenB+OMV NZ and MenABCWY vaccines. A total of 3651 healthy adolescents and young adults aged 10-25 years will be enrolled and randomised (5:5:3:3:3:1 ratio) to one of the six parallel study groups:

  – **MenB_0_2_6 group***: subjects will receive 3 doses of rMenB+OMV NZ at Day 1, Day 61 and Day 181 (0, 2 and 0,2,6-months schedule). These subjects will receive 1 dose of the MenACWY vaccine at Day 211**.

  – **MenB_0_6 group**: subjects will receive 2 doses of rMenB+OMV NZ at Day 1 and Day 181 and 1 dose of MenACWY vaccine at Day 61 (rMenB+OMV NZ, 0,6-months schedule). These subjects will receive 1 dose of placebo at Day 211**.

  – **ABCWY-1**: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 1 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211**.

  – **ABCWY-2**: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 2 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211**.

  – **ABCWY-3**: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 3 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211**.

  – **ACWY group**: subjects will receive 1 dose of MenACWY vaccine at Day 1, 1 dose of placebo at Day 61 and 2 doses of rMenB+OMV NZ at Day 181 and Day 211**.

  * MenB_0_2_6 group will also be evaluated for objectives pertaining to 0,2-months vaccination schedule.

  Note 1: A MenB lot will be used for the pre-filled syringe component of the MenABCWY vaccine.

  Note 2: The groups ABCWY-1, ABCWY-2, ABCWY-3 will be pooled into a single group, ABCWY (pooled lots) (except for analysis of lot to lot consistency).

  ** Note 3: In order to let the subjects in MenB_0_2_6 group receive a dose of MenACWY vaccine and for subjects in ACWY group to receive the second dose of rMenB+OMV NZ in line with the vaccine as standard of care (also in line with the Advisory Committee on Immunization Practices (ACIP) recommendations in the US [ACIP, 2011]), the subjects in these groups will receive a vaccination of MenACWY and rMenB+OMV NZ vaccines, respectively, on Day 211 (Visit 6) after completion of the post-vaccination 3 blood sampling. To maintain the blinding of the study, subjects in the rest of the groups (MenB_0_6, ABCWY-1, ABCWY-2 and ABCWY-3) will receive a dose of Placebo. All these vaccines/ product administered at Day 211 are not associated with any study objectives/ endpoints (Safety assessment

conducted after 1 dose of rMenB+OMV NZ in the ACWY group at Day 181 is to maintain the blind of the study).

- Duration of the study: The study duration is approximately 18 months for each subject.
- Primary completion Date (PCD): T10; Day 541.

Refer to Glossary of terms for the definition of PCD.

- End of Study (EoS): the date of release of the last testing results, to be achieved not later than 8 months after Last Subject Last Visit (LSLV) (LSLV = T10; Day 541). If the completion of testing occurs prior the completion of the LSLV the latter date defines the end of study visit.

Refer to Glossary of terms for the definition of EoS.

- Study groups:

Table 2 Study groups and treatment foreseen in the study

Study Groups	Number of subjects	Age (Min-Max)	Treatment name	Vaccine/Product name
MenB_0_2_6	912	10 – 25 y	*Bexsero* (Injection)	rMenB+OMV NZ
			Menveo (Injection)	MenACWY
MenB_0_6	912		*Bexsero* (Injection)	rMenB+OMV NZ
			Menveo (Injection)	MenACWY
			Placebo (Injection)	NaCl
ABCWY-1	548		MenABCWY (with Lot 1 of ACWY) (Injection)	MenABCWY-1
			Placebo (Injection)	NaCl
ABCWY-2	548		MenABCWY (with Lot 2 of ACWY) (Injection)	MenABCWY-2
			Placebo (Injection)	NaCl
ABCWY-3	548		MenABCWY (with Lot 3 of ACWY) (Injection)	MenABCWY-3
			Placebo (Injection)	NaCl
ACWY	183		*Menveo* (Injection)	MenACWY
			Placebo (Injection)	NaCl
			Bexsero (Injection)	rMenB+OMV NZ

Table 3 Overview of study design: Vaccination and Blood Draw Schedule

Visits **Study Day**	**Visit 1** **Day 1**	Visit 2 Day 31	**Visit** 3 **Day 61**	**Visit** 4 **Day 91**	**Visit** 5 **Day 181**	**Visit** 6 **Day 211**
Group **MenB_0_2_6** **N=912**	Pre-vacc Blood sample rMenB+OMV NZ	Post-vacc 1 Blood sample	rMenB+OMV NZ	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample MenACWY
Group **MenB_0_6** **N=912**	Pre-vacc Blood sample rMenB+OMV NZ	Post-vacc 1 Blood sample	MenACWY	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample Placebo
Group **ABCWY-1** **N=548**	Pre-vacc Blood sample MenABCWY-1	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-1	Post-vacc 3 Blood sample Placebo
Group **ABCWY-2** **N=548**	Pre-vacc Blood sample MenABCWY-2	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-2	Post-vacc 3 Blood sample Placebo
Group **ABCWY-3** **N=548**	Pre-vacc Blood sample MenABCWY-3	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-3	Post-vacc 3 Blood sample Placebo
Group **ACWY** **N=150**	Pre-vacc Blood sample MenACWY	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample rMenB+OMV NZ

N = number of subjects; Pre-vacc = pre-vaccination; Post-vacc = post-vaccination

- Treatment allocation: At Day 1, prior to the study vaccination, subjects will be randomised to 1 of the 6 study groups according to a 5:5:3:3:3:1 ratio.
- Blinding: Observer-blind. Kindly refer to Protocol Section 7.3 for details on blinding and unblinding procedures.
- Sampling schedule:
  - A total of 4 blood samples* will be collected from each subject at Day 1 (pre-vaccination blood sample; approximately 20 mL), at Day 31 (post-vaccination 1 blood sample; approximately 25 mL), at Day 91 (post-vaccination 2 blood sample; approximately 25 mL) and at Day 211 (post-vaccination-3 blood sample; approximately 25 mL).
  - Urine sampling: Urine samples for pregnancy testing will be collected from female subjects of child-bearing potential at Visit 1 (Day 1), Visit 3 (Day 61), Visit 5 (Day 181) and Visit 6 (Day 211) prior to the vaccination.

  * Insufficient blood volume may lead to test cancellation and jeopardise the statistical power. Hence, every effort must be done to collect blood volume as per protocol requirements.
- Data collection: standardised Electronic Case Report Form (eCRF). Solicited symptoms will be collected using a subject Diary (electronic Diary [eDiary]).
- Safety monitoring: Regular safety follow-up will be done through telephone calls (T). There will also be an extended safety follow-up (ESFU) phone call 12 months post-vaccination 3 (Day 181; Visit 5). This ESFU phone call will also mark the study conclusion. Refer to Protocol Table 3 and Protocol Section 8.5.3 for details on the safety follow-up.

3.3. Number of subjects

A total of 3651 subjects will be randomised in a ratio of 5:5:3:3:3:1; 912 each in MenB_0_2_6 and MenB_0_6 groups, 548 in each ABCWY groups and 183 in ACWY group. Assuming a 25% drop out rate, this should provide approximately 684 evaluable subjects in each of the MenB groups, 411 evaluable subjects in each of the ABCWY groups and 137 evaluable subjects in the ACWY group.

Refer to Protocol Section 10.1 for a detailed description of the criteria used in the determination of sample size.

Withdrawals will not be replaced.

3.4. Subject and study completion

A subject is considered to have completed the study, if the subject is available for the concluding contact (T10; Day 541) as described in the protocol.

Global completion of the study is required in order to provide enough subjects as defined in Protocol Section 10.1 Sample Size Determination.

4. ANALYSIS SETS

4.1. Definition

For purposes of analysis, the following analysis sets are defined:

4.1.1. Enrolled Set

Subject/ Subject for whom parent(s)/LAR's agreed to participate in a clinical study after completion of the informed consent process, who meet screening/eligibility criteria and randomized and/or received study intervention or undergone an invasive procedure.

4.1.2. Exposed Set

All subjects who received at least 1 dose of the study treatment. The allocation in a group is done in function of all administered treatments.

4.1.3. Full Analysis Set

All subjects who received at least 1 dose of the study treatment and have post-vaccination effectiveness or immunogenicity data.

4.1.4. Per Protocol Set

All subjects in the Full Analysis Set minus subjects with protocol deviations that lead to exclusion from the Per Protocol Set.

4.1.5. Solicited Safety Set

All subjects who received at least 1 dose of the study treatment (Exposed Set) who have solicited safety data beyond 30 minutes post vaccination.

4.1.6. Unsolicited Safety Set

All subjects who received at least 1 dose of the study treatment (Exposed Set) that report unsolicited AEs/report not having unsolicited AEs.

4.1.7. Overall Safety Set

All subjects that belong to the Unsolicited safety or/and to the Solicited safety set.

4.2. Criteria for eliminating data from Analysis Sets

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

4.2.1. Elimination from Exposed Set (ES)

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

4.2.2. Elimination from Per protocol Set (PPS)

4.2.2.1. Excluded subjects

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

Table 4 Elimination code and condition to exclude a subject from the PPS analysis

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
800	Fraudulent data	All	All
900	Invalid informed consent	All	All
1030	Study vaccine not administered at all	All	All
1050	Randomization failure	Visit 1, 3, 5	All
1060	Randomization code was broken	All	All
1070.1	Subjects got vaccinated with the correct vaccine but containing a lower volume	Visit 1, 3, 5	All
1070.2	Vaccination not according to protocol	Visit 1, 3, 5	All
1080	Vaccine temperature deviation	Visit 1, 3, 5	All
1090	Expired vaccine administered	Visit 1, 3, 5	All
1500.1	Other deviation from study procedures not able to classified under any other categories	All	All
1500.2	Any other GCP non-compliance not able to classified under any other categories	All	All
2010	Protocol violation (inclusion/exclusion criteria)	All	All
2040	Administration of any medication forbidden by the protocol	Visit 1, 3, 5	All
2050	Not withdrawn after developing withdrawal criteria other than prohibited concomitant vaccination/medication (medical condition forbidden)	All	All
2060	Concomitant infection related to the vaccine which may influence immune response (only meningococcal infection)	All	All
2080	Subjects did not comply with vaccination schedule	Visit 3, 5	All

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
2090	Subjects did not comply with blood sample schedule	Visit 2, 4, 6	All
2100	Serological results not available post-vaccination for all tests	Visit 2, 4, 6	All
2120	Obvious incoherence or abnormality or error in data related to testing	Visit 2, 4, 6	All
2130	Biological sample specimen procedures not compliant with protocol	Visit 2, 4, 6	All

4.2.3. Elimination from unsolicited and solicited safety set

4.2.3.1. Excluded subjects

4.2.3.1.1. Unsolicited safety set

Code 1030 (Study vaccine not administered at all), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1150 (no post-vaccination safety data) will be used for identifying subjects eliminated from the unsolicited safety set.

4.2.3.1.2. Solicited safety set

Code 1030 (Study vaccine not administered at all), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1160 (no post-vaccination solicited safety data) will be used for identifying subjects eliminated from the solicited safety set.

5. STATISTICAL ANALYSES

Standard data derivation rules and statistical methods are described in section 10.1 while the study specific data derivation rules and stat methods are described in section 9.

At the time of sign off of this SAP amendment, before start of enrolment of subjects, the impact of COVID-19 on the study is unclear. Additional analyses may be needed depending on the impact, and will be described in an updated SAP amendment.

5.1. Disposition of subjects

5.1.1. Analysis of disposition of subjects planned in the protocol

Number of subjects enrolled, vaccinated subjects (at least 1 vaccination, full vaccination course), reason for early withdrawal, FAS, and PPS will be described by vaccine group.

5.1.2. Additional considerations

Analyses of disposition of subjects will be repeated by age group (10-17 years of age and 18-25 years of age), race, sex and region (US region/ ex-US region).

5.2. Demography and baseline characteristics analyses

5.2.1. Analysis of demography and baseline characteristics planned in the protocol

Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age, height, weight, and body mass index (BMI) at enrolment will be calculated overall and by vaccine group.

Distributions of subjects by sex, race, ethnic origin will be summarised overall and by vaccine group.

5.2.2. Additional considerations

Analyses of demography and baseline characteristics will be repeated by age group (10-17 years of age and 18-25 years of age), race, sex and the US region.

5.3. Primary effectiveness and immunogenicity

5.3.1. Analysis of primary effectiveness and immunogenicity planned in the protocol

Refer to Glossary of terms for definitions of test-based and responder-based vaccine effectiveness.

5.3.1.1. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Analysis set: Per-protocol set (PPS) will be the primary analysis population

Statistical method: The VE is defined as 1- RR= (1- percentage of samples without bactericidal serum activity at 1:4 dilution in MenB group / percentage of samples without bactericidal serum activity at 1:4 dilution in the ACWY group) x100% and it will be analyzed using a generalised linear model with vaccine group, strain and center as independent variables. Furthermore, a repeated statement will be used to estimate the variance of the RR including correlation within subject's responses to different strains. A center effect will be tentatively included in the analysis; if the statistical model does not converge due to the factor "center", a model without center effect will be fitted instead. In case some centers within a country have a small number of subjects, the centers may be pooled. The response variable of the model will be the Bernoulli distributed outcome without bactericidal activity at a 1:4 dilution (i.e. response is 1 if titre < 4, and 0 if titre ≥ 4), at 1 month after the last vaccination (Month 7) in the MenB group and at Month 1 for

the ACWY group. Each subject will contribute with approximately 35 measures to this analysis, each of the measures corresponding to the response variable to one of the 35 strains randomly assigned to be tested with the samples available for that specific subject. For the statistical analysis it is assumed that for each strain the response is an independent measure between subjects with a unique true underlying strain-specific rate and VEs are expected to vary among the strains. In order to obtain the VE measure which is a measure based on the relative risk (RR), a generalised linear model will be used with the Binary distribution and link function log in order to compute the log RR and the corresponding 97.5% CI. If this model would not converge, the Poisson distribution will be used instead. The obtained values will be exponentiated to obtain the RR and the corresponding 97.5% CI. The VE will be computed as 100% x (1 – RR). Effectiveness of rMenB+OMV NZ will be demonstrated if the lower limit of the two-sided 97.5% CI for VE against the selected strain panel between MenB and the ACWY group is above 65%.

5.3.1.2. Effectiveness (Responder-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Analysis set: FAS will be the primary analysis population.

Statistical method: The percentage of responders (see definition in Glossary of terms) and the corresponding exact two-sided 97.5% CI based on Clopper-Pearson method will be calculated [Clopper, 1934].

The objective is to demonstrate that the lower limit of the 97.5% CI for the percentage of responders is higher than 65%.

5.3.1.3. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 5.3.1.1

5.3.1.4. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 5.3.1.2

5.3.1.5. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 5.3.1.1

5.3.1.6. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 5.3.1.2

5.3.1.7. Lot-to-lot consistency: MenABCWY - ACWY component

Analysis set: The analysis of lot-to-lot consistency will be based on the PPS.

Statistical method: For each of the three ABCWY lots (Lots 1, 2 and 3 of the MenACWY component of the ABCWY vaccine), GMTs and 97.5% CIs will be calculated by exponentiating (base 10) the least squares means and the lower and upper limits of the 97.5% CIs of the log transformed titres (base10) obtained from a two-way Analysis of Variance (ANOVA) with factors for vaccine lot and study center. Additionally, lot-to-lot GMT ratios will be computed for each pair of ABCWY lots. Ninety-seven point five percent (97.5%) CIs for the ratios of GMTs will be constructed by exponentiating the difference of the least square means of the log transformed titres and the lower and upper limits of the 97.5% CIs on the difference obtained from the ANOVA model above.

Lot-to-lot consistency criterion: The three ABCWY lots will be considered equivalent if for each of the 4 serogroups A, C, W and Y and each pair of vaccine lots, the two-sided 97.5% CI on the ratio of GMTs at 1 month after the last vaccination will be contained within the interval [0.5, 2.0]

5.3.1.8. Immunological non-inferiority: MenABCWY vs. MenACWY

Analysis set: PPS will be the primary analysis population.

Statistical method: The percentage of subjects with 4-fold rise* in hSBA titres against MenACWY indicator strains A, C, W and Y and the corresponding exact two-sided 97.5% CIs based on Clopper-Pearson method will be calculated for the ABCWY (pooled lots) group and the ACWY group [Clopper, 1934]. The 97.5% CIs for the difference in percentages between ABCWY (pooled lots) and ACWY group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-Inferiority criterion: Non-inferiority of MenABCWY vaccine for the proportion of subjects with 4-fold rise will be demonstrated if the lower limit of the two-sided 97.5% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY (pooled) lots –ACWY) is above -10%.

* For the Men A, C, W, Y evaluation, the 4-fold rise is defined as:

- a post-vaccination hSBA titre ≥16 for subjects with a pre-vaccination hSBA titre <4
- a post-vaccination hSBA titre ≥4 times the LLOQ for subjects with a pre-vaccination hSBA titre ≥LOD but <LLOQ, and
- a post-vaccination hSBA titre ≥4 times the pre-vaccination titre for subjects with a pre-vaccination hSBA titre ≥LLOQ.

5.3.1.9. Vaccine effectiveness (Test-based): MenABCWY

See Section 5.3.1.1

5.3.1.10. Effectiveness non-inferiority: MenABCWY vs. rMenB+OMV NZ

Analysis set: PPS will be the primary analysis population.

Statistical method: The percentage of samples with bactericidal activity measured by enc-hSBA at 1:4 dilution and the corresponding exact two-sided 97.5% CIs based on Clopper-Pearson method will be calculated for the ABCWY (pooled lots) group and the MenB group comparator that will be selected (ref: the footnote of Figure 2). The 97.5% CIs for the difference in percentages between ABCWY (pooled lots) and selected MenB group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-Inferiority criterion: Non-inferiority of MenABCWY vaccine for the percentage of samples with bactericidal activity measured by enc-hSBA at 1:4 dilution will be demonstrated if the lower limit of the two-sided 97.5% CI for the difference between the 2 groups (ABCWY (pooled) lots – MenB) is above -5%.

5.3.1.11. Effectiveness (Responder-based): MenABCWY

See Section 5.3.1.2

5.3.2. Additional considerations

Analyses of the primary objectives will be repeated by age group (10-17 years of age and 18-25 years of age), race, sex and the US region.

5.3.2.1. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

The SAS code to analyse the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) objective is specified below. Treatment, center, and strains will be modelled as fixed effect. In order to account for a possible over-dispersion, the DSCALE option in the model statement will be evaluated first. The DSCALE will be kept in the model only if the F-statistics for the DSCALE parameter is significant ($p<0.05$). The following SAS code will be used for the VE calculation:

```
ods trace on;
ods output  GEEEmpPEst  = genmod_stats
CONVERGENCESTATUS = converge ;

PROC GENMOD data=dataset descending;
class trtgrp strain center subject_id ;
model outcome = trtgrp strain center / dist= bin link= log DSCALE
alpha=0.025;
repeated subject = subject_id / type= UN ;
estimate 'Beta' trtgrp 1 0 0 0 0 -1/ exp;

/*trtgrp R is MenB0,2,6 and trtgrp W is ACWY*/

run;
```

```
ods output close;

data genmod_stats;
set genmod_stats;
where parm = 'trtgrp' and level1 = '1';
rr = exp(estimate);
ub = exp(uppercl);
ve = (1 - rr)*100 ;
ve_ll = (1 - ub) * 100 ;
if ve_ll > 65 then success = 1 ;
else success = 0 ;
run;
```

where outcome represents the Bernoulli distributed outcome without bactericidal activity at a 1:4 dilution (i.e. response is 1 if titre < 4, and 0 if titre ≥ 4), one month after the 3rd vaccination in MenB 0,2,6 and one month after the MenACWY vaccination for the ACWY arm, trtgrp indicates the vaccine groups, strain is the serogroup B strain variable, and center is the site.

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

rr is the relative risk (RR), which is obtained from the estimated parameters from PROC GENMOD. Vaccine effectiveness (VE) is then derived as (1-rr)x100%.

ub represents the upper bound of the 97.5% CI of the relative risk. ve_ll is the lower bound of the 97.5% CI for VE, if the value is greater than 65%, then the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) objective is successful.

5.3.2.2. Effectiveness (Responder-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Not applicable

5.3.2.3. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 5.3.2.1, with the difference in the treatment arm:

```
PROC GENMOD data=dataset descending;
class trtgrp strain center subject_id ;
model outcome = trtgrp strain center / dist= bin link= log DSCALE
alpha=0.025 ;
repeated subject = subject_id / type= UN ;
estimate 'Beta' trtgrp 0 1 0 0 0 -1/ exp;

/*trtgrp S is MenB0,6 and trtgrp W is ACWY*/

run;
```

5.3.2.4. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

Not applicable

5.3.2.5. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 5.3.2.1, with the difference the outcome data for group R is from one month after the 2nd vaccination instead of one month after the 3rd vaccination.

5.3.2.6. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

Not applicable

5.3.2.7. Lot-to-lot consistency: MenABCWY - ACWY component

Not applicable

5.3.2.8. Immunological non-inferiority: MenABCWY vs. MenACWY

Not applicable

5.3.2.9. Vaccine effectiveness (Test-based): MenABCWY

See Section 5.3.2.1, with the difference in the estimate statement:

```
PROC GENMOD data=dataset descending;
class trtgrp strain center subject_id ;
model outcome = trtgrp strain center / dist= bin link= log DSCALE
alpha=0.025 ;
repeated subject = subject_id / type= UN ;
estimate 'Beta' trtgrp 0 0 1 1 1 -3/ exp divisor=3;

/*trtgrp T, U, and V are the ABCWY-1, ABCWY-2, and ABCWY-3 lots and
trtgrp W is ACWY*/
run;
```

5.3.2.10. Effectiveness non-inferiority: MenABCWY vs. rMenB+OMV NZ

Not applicable

5.3.2.11. Effectiveness (Responder-based): MenABCWY

Not applicable

5.4. Secondary effectiveness and immunogenicity

5.4.1. Analysis of secondary effectiveness and immunogenicity planned in the protocol

5.4.1.1. Immunological non-inferiority: MenABCWY vs. rMenB+OMV NZ

Analysis set: PPS will be the primary analysis population.

Statistical method: The percentages of subjects with 4-fold rise** in hSBA titres against N. meningitidis serogroup B indicator strains (M14459, 96217, M07-0241084* and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively) at 1 month after the last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) and 1 month after the 3-dose vaccination series (Day 211, Month 7) in MenB_0_2_6 group or 2-dose vaccination series (Day 211, Month 7) in MenB_0_6 group or 2-dose vaccination series (Day 91, Month 3) in MenB_0_2_6 group and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated [Clopper, 1934]. The 95% CIs for the difference in percentages between ABCWY group (pooled lots) and MenB_0_2_6 group and MenB_0_6 group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-inferiority criterion: Non-inferiority of MenABCWY vaccine for the proportion of subjects with 4-fold rise will be demonstrated if the lower limit of the 2-sided 95% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY group (pooled lots) –selected MenB group) is above -10%.

* The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented either in a protocol amendment or in the clinical report.

** For the MenB evaluation, the 4-fold rise per each indicator strain is defined as:

- a post-vaccination‡ hSBA titre ≥16 for subjects with a pre-vaccination hSBA titre <4
- a post-vaccination‡ hSBA titre ≥4 times the LLOQ for subjects with a pre-vaccination hSBA titre ≥LOD and <LLOQ, and
- a post-vaccination‡ hSBA titre ≥4 times the pre-vaccination hSBA titre for subjects with a pre-vaccination hSBA titre ≥ LLOQ

‡ = post-2nd vaccination for 0,6 and 0,2 schedule and post-3rd vaccination for 0,2,6 schedule).

5.4.1.2. Effectiveness by each of the endemic US N. meningitidis serogroup B strains

Analysis set: FAS will be the primary analysis population. A subset (VE subset) of approximately 684 evaluable subjects per group, ABCWY (pooled lots) and of the MenB_0_2_6 or MenB_0_6 group would be used for the purpose of this analysis.

Statistical method: The VE per strain will be calculated as described in Section 5.3.1.1, using a generalised linear model with vaccine group, and center as independent variables, and alpha=0.05 leading to 95% CI. In case for a strain 100% response will be observed in both vaccine groups, VE against these strain will be assessed by calculating 95% CI for relative risk from raw proportions, and VE=1-RR.

5.4.1.3. Distribution of percentages of serogroup B invasive disease strains killed

Analysis set: FAS will be the primary analysis population. A subset (VE subset) of approximately 684 evaluable subjects per group, ABCWY (pooled lots) and of the MenB_0_2_6 or MenB_0_6 group would be used for the purpose of this analysis.

Statistical method: The distribution will be presented of subjects by percentages of serogroup B invasive disease strains killed using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series of rMenB+OMV NZ and MenABCWY vaccines.

Summary statistics and 95% CI for the mean percentage will be presented, as well as a Figure of the cumulative distribution function.

5.4.1.4. Immune response of MenABCWY, rMenB+OMV NZ and MenACWY

Analysis set: The analysis will be based on the FAS.

Statistical method: The hSBA titres at each time point for all groups (ABCWY group (pooled lots), MenB_0_2_6 and MenB_0_6 groups) will be logarithmically transformed (base10) to fulfil the normal distribution assumption. For each N. meningitidis serogroup A, C, W and Y and each B indicator strain (M14459, 96217, M07-0241084* and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively), the GMTs and GMRs (post-vaccination/baseline) will be obtained from a two-way Analysis of Variance (ANOVA) with factors for vaccine group and study center, and then exponentiating the log-transformed means and their 95% CIs. The ratio of GMTs and GMRs between two groups and the corresponding CI will be estimated additionally.

The total IgG as measured by ELISA GMCs against serogroups A, C, W and Y at baseline (Day 1, Month 0) and

- at 1 month after the first (Day 31, Month 1) and the last vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and

- at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1),

will be analyzed in a comparable way as described above for hSBA titres.

For each N. meningitidis A, C, W and Y and for each (individual response) and all (composite response serogroup B indicator strain (M14459, M07-0241084*, 96217and NZ98/254) the percentages of subjects with hSBA titres ≥ LLOQ and of subjects with 4-fold rise and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated for each study group at each timepoint not previously analyzed. Ninety-five percent (95%) CIs for the difference in percentages between ABCWY (pooled lots) on the one hand and MenB_0_2_6, MenB_0_6, and ACWY groups, respectively, on the other hand, will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

* The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented either in a protocol amendment or in the clinical report.

5.4.2. Additional considerations

5.4.2.1. Immunological non-inferiority: MenABCWY vs. rMenB+OMV NZ

Not applicable

5.4.2.2. Effectiveness by each of the endemic US N. meningitidis serogroup B strains

The SAS code to analyse the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) by strain is specified below. Treatment, center will be modelled as fixed effect. In order to account for a possible over-dispersion, the DSCALE option in the model statement will be evaluated first. The DSCALE will be kept in the model only if the F-statistics for the DSCALE parameter is significant ($p<0.05$). The following SAS code will be used for the VE calculation:

```
ods trace on;
ods output  GEEEmpPEst = genmod_stats
CONVERGENCESTATUS = converge ;

PROC GENMOD data=dataset descending;
class trtgrp center ;
by strain ;
model outcome = trtgrp center / dist= bin link= log DSCALE alpha=0.05;
estimate 'Beta' trtgrp 1 0 0 0 0 -1/ exp;

/*trtgrp R is MenB0,2,6 and trtgrp W is ACWY*/

run;

ods output close;
```

```
data genmod_stats;
set genmod_stats;
by strain ;
where parm = 'trtgrp' and level1 = '1';
rr = exp(estimate);
ub = exp(uppercl);
ve = (1 - rr)*100 ;
ve_ll = (1 - ub) * 100 ;
if ve_ll > 65 then success = 1 ;
else success = 0 ;
run;
```

where outcome represents the Bernoulli distributed outcome without bactericidal activity at a 1:4 dilution (i.e. response is 1 if titre < 4, and 0 if titre ≥ 4), one month after the 3rd vaccination in MenB0,2,6 and one month after the MenACWY vaccination for the ACWY arm, trtgrp indicates the vaccine groups, strain is the serogroup B strain variable, and center is the site.

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

rr is the relative risk (RR), which is obtained from the estimated parameters from PROC GENMOD. Vaccine effectiveness (VE) is then derived as (1-rr)x100%.

ub represents the upper bound of the 95% CI of the relative risk. ve_ll is the lower bound of the 95% CI for VE, if the value is greater than 65%, then the Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule) objective is successful.

In summary in case of convergence issue the following hierarchical decision tree will be applied

- Binary model including center effect

- Poisson regression including center effect

- Binary model, excluding center effect

- Poisson regression, excluding center effect

- Cochran-Mantel-Haenszel (CMH) method (if strain has 100% killed or 0% killed for ANY treatment)

- VE set to 0% (if strain has 100% killed for both treatment)

5.4.2.3. Distribution of percentages of serogroup B invasive disease strains killed

Not applicable

5.4.2.4. Immune response of MenABCWY, rMenB+OMV NZ and MenACWY

Not applicable

5.5. Safety and reactogenicity

5.5.1. Analysis of safety and reactogenicity planned in the protocol

Distribution of subjects by vaccinations will be summarised by vaccine group for the Enrolled Set. In case of vaccination error, subjects will be analyzed "as treated" (according to the vaccine the subject received).

Analysis sets: Solicited Safety Set (solicited local and systemic adverse events and other solicited adverse events), Unsolicited Safety Set (unsolicited adverse events), and Overall Safety Set.

Endpoint	Statistical Analysis Methods
Primary	**Endpoints description**: The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) adverse events during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. All solicited adverse events will be summarised according to defined severity grading scales, see protocol section 12.5.9.3. Frequencies and percentages of subjects experiencing each adverse event will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic adverse event overall and at each time point will also be presented. Post-vaccination solicited adverse events reported from Day 1 to Day 7 will be summarised for the intervals Day 1-3, Day 4-7, and Day 1-7 by maximal severity and by vaccine group, excluding the 30-minute measurement, which will be summarised separately. The severity of solicited local adverse events, including redness (erythema) at injection site, swelling of skin at injection site, and hardness of skin at injection site will be summarised according to categories based on linear measurement: None (1 to 24mm); Mild (25 to 50mm); Moderate (51 to 100mm); Severe (>100mm). Injection site tenderness and systemic reactions (except fever) occurring up to 7 days after each vaccination at Day 1, Day 61 and Day 181 will be summarised according to "mild", "moderate" or "severe". Each solicited local and systemic adverse event will also be further summarised as "none" versus "any" (for fever the latter will be ≥38.0 °C). Use of antipyretics and analgesics will be summarised by frequency by type of use (prophylactic versus treatment) and percentage of subjects reporting use. Body temperature will be summarised 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 temperatures ≥ 38.0 °C and temperatures ≥ 40.0 °C will also be presented.
	Endpoints description: The frequencies and percentages of subjects with any unsolicited ***AEs*** (including all SAEs), ***AEs*** leading to withdrawal and medically attended ***AEs*** during the 7 and the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. The frequencies and percentages of subjects with SAEs, ***AEs*** leading to withdrawal***, AESIs*** and medically attended ***AEs*** throughout the study period. This analysis applies to all adverse events occurring during the study, judged either as possibly related, or not related to vaccination by the investigator, recorded in AE CRF, with a start date on

Endpoint	Statistical Analysis Methods
	or after the date of first vaccination. AE starting prior to the first vaccination will only be listed. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class. All reported adverse events, as well as adverse events judged by the investigator as possibly related to study vaccine, will be summarised 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 adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted. Separate summaries will be produced for the following categories: • Serious adverse events. • Adverse events that are possibly related to vaccine. • Adverse events of special interest. • Adverse event leading to withdrawal. • Adverse events leading to a medically attended visit. Data listings of all adverse events will be provided by subject. In addition, adverse events in the categories above will be provided as listed data. Local and systemic AEs will be analyzed by point estimates with associated 95% CIs [Clopper, 1934].

5.5.2. Additional considerations

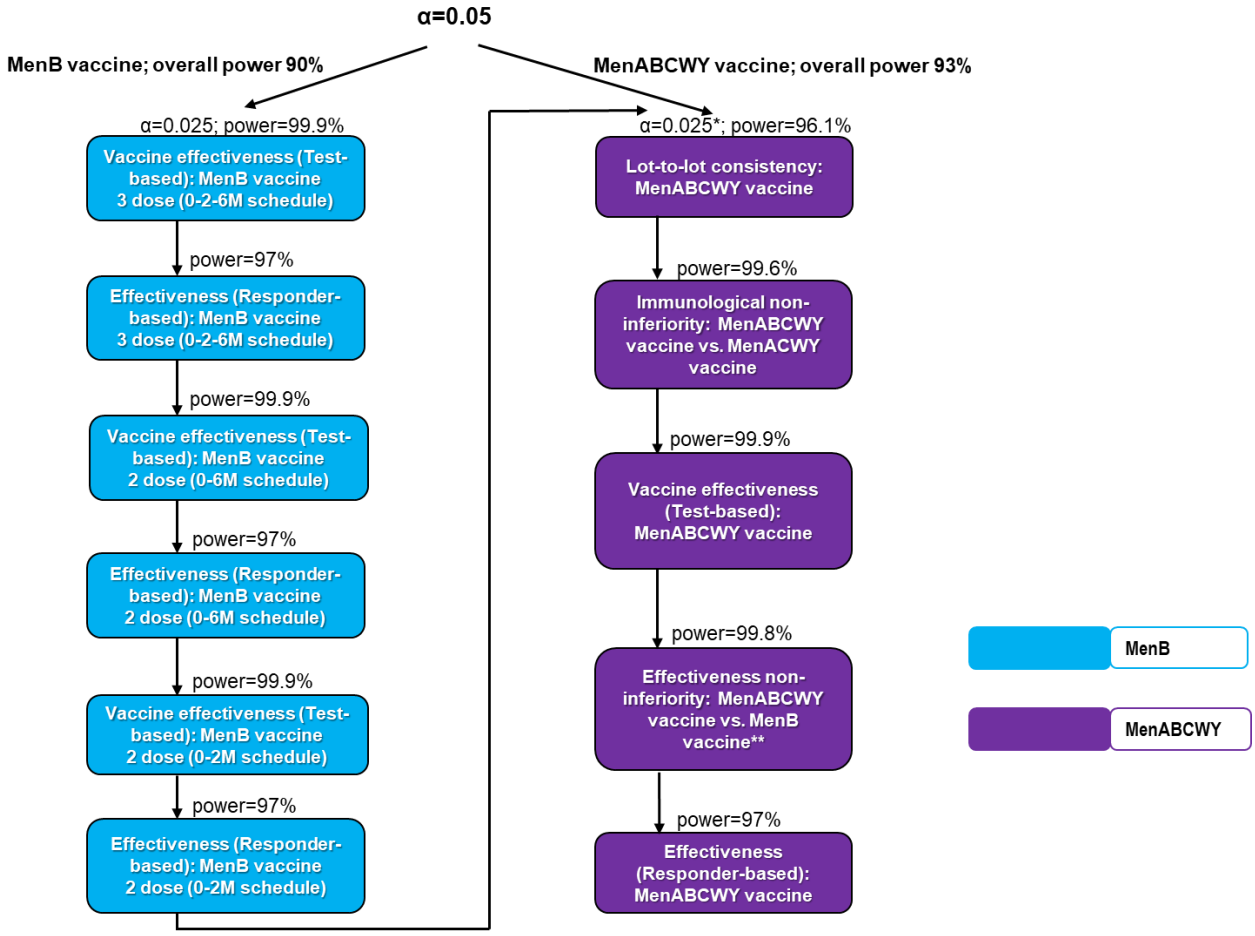
For analyses of the safety and reactogenicity endpoints, subjects will be analyzed "as treated" according to the actual vaccination a subject received.

6. ANALYSIS INTERPRETATION

Multiple objectives and endpoints require type I error control. Full alpha (0.05) is split equally (alpha=0.025) between rMenB+OMV NZ objectives and MenABCWY objectives. Furthermore, within rMenB+OMV NZ, as well as within MenABCWY, objectives are tested hierarchically. If the first null hypothesis is rejected, then the testing will continue with the second hypothesis at same alpha. Same for 3rd, 4th, and so forth. Whenever a null hypothesis is not rejected, then the testing will stop.

As the comparator for MenABCWY non inferiority objective for the B component will be the selected schedule of rMenB+OMV NZ as determined in this study, the objectives of rMenB+OMV NZ will be analysed first. Additionally, if all null hypotheses related to rMenB+OMV NZ objectives will be rejected, the alpha (alpha=0.025) will be propagated to the MenABCWY part, and hypotheses related to MenABCWY objectives will be tested at full alpha (alpha=0.05). See Figure 2 for an explanation of the hierarchical testing (top to bottom, the order indicated by the arrows).

Figure 2 Hierarchical testing of hypothesis



* Alpha split equally between rMenB+OMV NZ and MenABCWY vaccine objectives.
If all rMenB+OMV NZ objectives achieved, MenABCWY vaccine objectives will be tested at full alpha.
** If all objectives of rMenB+OMV NZ are met, the comparator will be the 0,2-months schedule. If the 0,2-months objective is not met, and the 0,6-months is met, then the 0,6-months schedule will be the comparator. If the 0,6-months is also not met, then the 0,2,6-months schedule will be the comparator.

Refer to Glossary of terms for definitions of test-based and responder-based vaccine effectiveness.

7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

The final study report will contain at least the final analyses of all primary and secondary endpoints.

7.2. Statistical considerations for interim analyses

No interim analysis is planned for this study

8. CHANGES FROM PLANNED ANALYSES

Not applicable

9. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

The following sections describe additional derivation rules and statistical methods which are not presented in section 10.1.

9.1. Data derivation

Not applicable

9.2. Statistical Method

Not applicable

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

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

10.1.1. Attributing events to vaccine doses

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

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

10.1.2. Handling of missing data

10.1.2.1. Dates

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

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

The following exceptions apply:

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

year. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that year.

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

10.1.2.2. Laboratory data

Missing laboratory results (including immunological data) will not be replaced.

10.1.2.3. Daily recording of solicited adverse events

10.1.2.3.1. Studies with electronic diaries

For studies using electronic diaries for the collection of solicited adverse events, a solicited adverse events will be considered present only when a daily recording of grade 1 or more is present.

10.1.2.4. Unsolicited adverse events

Unsolicited adverse event summaries are including serious adverse events unless specified otherwise.

Missing severity, relationship with study vaccine, and outcome of unsolicited adverse events will not be replaced and will appear as 'UNKNOWN' in all statistical output.

10.1.3. Data derivation

10.1.3.1. Age at vaccination in days

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

Age = date of vaccination minus date of birth

10.1.3.2. Age at vaccination in months

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

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

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

10.1.3.3. Age at vaccination in years

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

DOB = 10SEP1983, Date of vaccination = 09SEP2018 -> Age = 34 years

DOB = 10SEP1983, Date of vaccination = 10SEP2018 -> Age = 35 years

10.1.3.4. Weight

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

Weight in kilograms = Weight in pounds / 2.2

10.1.3.5. Height

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

Height in centimeters = Height in inches x 2.54

10.1.3.6. Body mass index (BMI)

BMI will be calculated as follows:

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

10.1.3.7. Temperature

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

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

10.1.3.8. Numerical serology results

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

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

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

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

10.1.3.10. Onset day

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

10.1.3.11. Duration of events

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

The duration of solicited events will be calculated as the sum of the individual days with the adverse event reported at grade 1 or higher during the solicited adverse event period.

10.1.3.12. Counting rules for combining solicited and unsolicited adverse events

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

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

10.1.3.13. Counting rules for occurrences of solicited adverse events

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

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with:

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

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

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

10.1.4.2. Differences in percentages

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

10.1.4.3. Demographic/baseline characteristics statistics

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

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

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

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

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

10.1.4.4. Serological summary statistics

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

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

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

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

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

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

10.1.5.2. Standardized asymptotic confidence intervals around differences in proportions

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

10.2. TFL TOC

The Tables Figures and Listings (TFL) Table of Contents (TOC) which itemizes the planned list of TFL and their associated lay-out is developed as a separate document.

10.3. Glossary of terms

End of Study (EoS) **(Synonym of End of Trial)**	For studies with collection of human biological samples and/or imaging data, the EoS is defined as Last subject last visit (T10). or Last testing results released of samples collected at Visit 6* * In this case EoS must be achieved no later than 8 months after LSLV.
Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.
Responder-based vaccine effectiveness:	The enc-hSBA methodology involves testing the serum samples from each individual subject against a subset of around 35 strains randomly chosen from the overall panel of 110 meningococcus B US strains. Responder-based vaccine effectiveness is assessed based on the percentage of subjects considered responders, i.e., subjects whose serum kills the majority (≥70% in this study) of the tested strains following vaccination.
Test-based vaccine effectiveness:	The enc-hSBA methodology involves testing the serum samples from each individual subject against a subset of around 35 strains randomly chosen from the overall panel of 110 meningococcus B US strains. Test-based vaccine effectiveness is assessed based on the overall percent of individual positive tests following vaccination and represents the reduction in risk compared to the placebo.

11. REFERENCES

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Clopper CJ, Pearson E. The Use of Confidence or Fiducial Limits Illustrated in the case of the Binomial. *Biometrika.* 1934;26:404-13.

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

	Statistical Analysis Plan
Detailed Title:	A phase 3b, randomized, controlled, observer-blind, multi-center study assessing the effectiveness and safety of GSK's meningococcal Group B vaccine administered to healthy adolescents and young adults.
eTrack study number and Abbreviated Title	205416 [MENB REC 2ND GEN-038 (V72_72)]
Scope:	All data pertaining to the above study.
Date of Statistical Analysis Plan	Final: 25 July 2019

APP 9000058193 Statistical Analysis Plan Template V4 (Effective date: 3 June 2019)

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LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
AESI	Adverse Events of Special Interest
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BMI	Body Mass Index
CI	Confidence Interval
CL	Confidence Limit
eCRF	Electronic Case Report Form Electronic Case Report Form
eDiary	Electronic Diary
Eli Type	Internal database code for type of elimination code
Enc-hSBA	Endogenous complement human Serum Bactericidal Assay
EoS:	End of Study
ES	Exposed Set
eTMF	Electronic Trial Master File
FAS	Full Analysis Set
fHbp	Factor H binding protein
GMR	Geometric mean ratio
GMR	Geometric mean ratio
GMT	Geometric mean antibody titer
GSK	GlaxoSmithKline
hSBA	Human Serum Bactericidal Assay
LL	Lower Limit
LLOQ	Lower Limit of Quantitation
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
N. meningitidis	*Neisseria* meningitidis
NA	Not Applicable
NadA	*Neisseria* adhesin A
NHBA	*Neisseria* Heparin Binding Antigen
OMV	Outer Membrane Vesicles
PCD	Primary Completion Date

PD	Protocol Deviation
PorA	Porin Protein A
PPS	Per-Protocol Set
rMenB+ OMV NZ	Recombinant Meningococcal B with Outer Membrane Vesicle derived from *Neisseria meningitidis* serogroup B strain NZ98/254 (New Zealand strain) Vaccine
RR	Relative Risk
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBIR	Source data Base for Internet Randomization
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
SR	Study Report
SUSAR	Suspected Unexpected Serious Adverse Reaction
TFL	Tables Figures and Listings
TOC	Table of Contents
UL	Upper Limit

1. DOCUMENT HISTORY

Date	Description	Protocol Version
25 JUL 2019	Final version	Amendment 1: 23 MAY 2019

2. OBJECTIVES/ENDPOINTS

Table 1 Study objectives and endpoints

Objectives	Endpoints
Primary	
To assess the effectiveness of the rMenB+OMV NZ vaccine against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity using enc-hSBA at one month after the 2-dose (0-,2-M; 0-,6-M) and 3-dose (0-,2-,6-M) vaccination series when compared to the Control Group in adolescent and young adult subjects. Criterion to demonstrate effectiveness of rMenB+OMV NZ vaccine: lower limit of the two-sided 95% confidence interval (CI) for vaccine effectiveness against a randomly selected strain panel between the rMenB+OMV NZ and the Control group is above 40%.	• The percentage of subjects without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at one month after the 2-dose (0-,2-M; 0-, 6-M) and 3-dose (0-,2-,6-M) vaccination series. The percentages of subjects will be averaged across all strains.
The study is considered a success if the criterion to demonstrate effectiveness is met for at least one of the vaccination schedules.	
Secondary	
To assess the effectiveness of the rMenB+OMV NZ vaccine against each of the randomly selected endemic US *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity using enc-hSBA at one month after the 2-dose (0-,2-M; 0-,6-M) and 3-dose (0-,2-,6-M) vaccination series, when compared to the Control Group in adolescent and young adult subjects.	• The percentage of subjects without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at one month after the 2-dose (0-,2-M; 0-, 6-M) and 3-dose (0-,2-,6-M) vaccination.
To describe the distribution of subjects by percentages of serogroup B invasive disease strains killed using enc-hSBA at one month after the 2-dose (0-,2-M; 0-,6-M) and 3-dose (0-,2-,6-M) vaccination series.	• The percentage of serogroup B invasive disease strains killed using enc-hSBA in each subject, at one month after the 2-dose (0-,2-M; 0-,6-M) and 3-dose (0-,2-,6-M) vaccination series.
To assess the percentages of subjects whose sera kill ≥70% of strains tested using enc-hSBA at one month after the 2-dose (0-,2-M; 0-,6-M) and 3-dose (0-,2-,6-M) vaccination.	• The percentages of subjects whose sera kill ≥70% of the strains tested using enc-hSBA, at one month after the 2-dose dose (0-,2-M; 0-,6-M) and 3-dose (0-,2-,6-M) vaccination series.
To assess the immune response to rMenB+OMV NZ vaccine against *N. meningitidis* serogroup B test strains M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA) and M07-0241084 (NHBA), at one month after the 2-dose (0-,2-M; 0-,6-M) and 3-dose (0-,2-,6-M) vaccination series, when compared to the Control Group.	The immune response to rMenB+OMV NZ vaccine will be evaluated by measuring bactericidal activity against *N. meningitidis* serogroup B test strains as following: • The percentage of subjects with hSBA titers ≥ lower limit of quantitation (LLOQ) for each and all serogroup B test strains at baseline and at one month after the 2-dose (0-,2-M; 0-,6-M) and 3-dose (0-,2-,6-M) vaccination series. • The percentage of subjects with fourfold increase in hSBA titers one month after the 2-dose (0-,2-M;

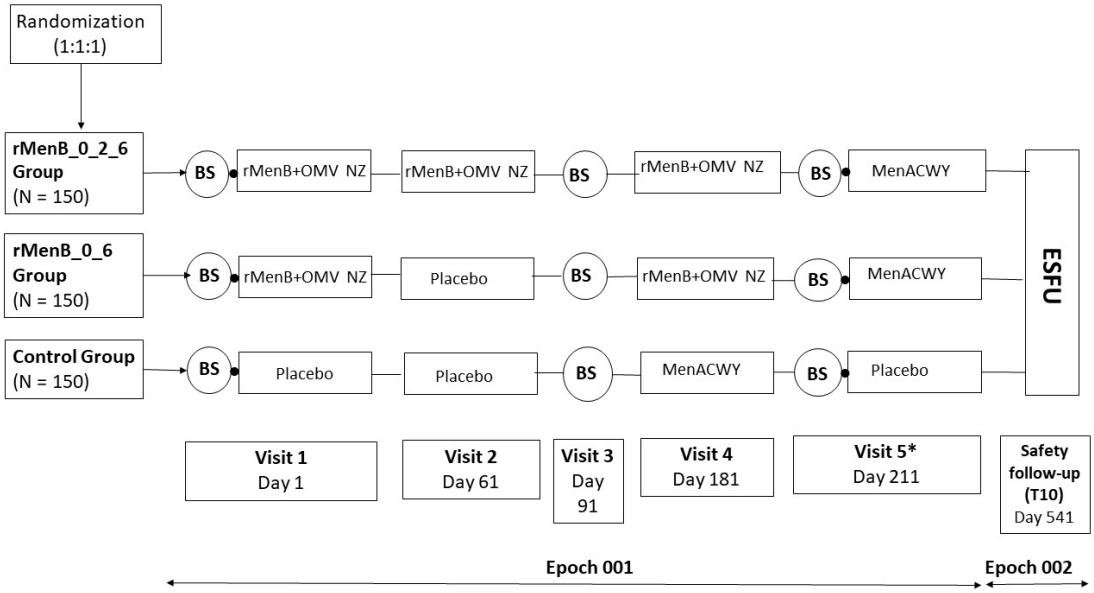
Objectives	Endpoints
	0-,6-M) and 3-dose (0-,2-,6-M) vaccination series relative to baseline defined as: ○ If the baseline titer is <limit of detection (LOD), then post-vaccination titer should be ≥ 4x LOD or ≥LLOQ, whichever is greater ○ If the baseline titer is ≥LOD but <LLOQ, then post-vaccination titer should be ≥4x LLOQ ○ If the baseline titer is ≥LLOQ, then post-vaccination titer should be ≥ 4x the baseline titer • Geometric mean titers (GMTs) at baseline and at one month after the 2-dose (0-,2-M; 0-,6-M) and 3-dose (0-,2-,6-M) vaccination series and geometric mean ratios (GMRs) at one month after 2-dose (0-,2-M; 0-,6-M) and 3-dose (0-,2-,6-M) vaccination series as compared to the baseline.
To evaluate the safety and reactogenicity of the rMenB+OMV NZ and MenACWY vaccines in adolescent and young adult subjects.	• The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) adverse events during the 7 days (including the day of vaccination) following vaccination at Day 1, Day 61 and Day 181. • The frequencies and percentages of subjects with any unsolicited AEs (including all SAEs), AEs leading to withdrawal and medically attended AEs during the 7 and the 30 days (including the day of vaccination) following vaccination at Day 1, Day 61 and Day 181. • The percentages of subjects with SAEs, AEs leading to withdrawal, AESIs and medically attended AEs throughout the study period.

M = Month; AE = Adverse event; SAE = Serious adverse event; AESI = Adverse event of special interest

3. STUDY DESIGN

The purpose and aim of this study, MENB REC 2ND GEN-038 (V72_72), is to evaluate the effectiveness, immunogenicity and safety of 2 doses or 3 doses of rMenB+OMV NZ vaccine in adolescents and young adults by measuring the bactericidal serum activity against endemic US *N. meningitidis* serogroup B strains using an enc-hSBA, when compared to the Control Group.

Figure 1 Study design overview



N = number of subjects; BS = Blood Sample; ESFU = Extended Safety Follow-Up; T=Telephone call

* In order to let the subjects in rMenB_0_2_6 and rMenB_0_6 groups receive a dose of MenACWY vaccine in line with Advisory Committee on Immunization Practices (ACIP) recommendations, the subjects in these groups will receive a vaccination of MenACWY on Day 211 (Visit 5) after completion of the post-vaccination 3 blood sampling. To maintain the blinding of the study, subjects in the Control Group will receive a dose of Placebo. At this time point, the vaccine/ product is not associated with any study objectives/ endpoints.

Type of study: Self-contained.

Experimental design: This is a phase 3b, randomized, controlled, observer-blind, multi-center study to evaluate effectiveness, immunogenicity and safety of rMenB+OMV NZ vaccine. Approximately 450 healthy adolescents and young adults aged 10-25 years will be enrolled and randomized (1:1:1 ratio) to one of the three study groups:

- rMenB_0_2_6 group*: subjects receiving 3 doses of rMenB+OMV NZ vaccine at Day 1, Day 61 and Day 181 (0-, 2- and 6-M schedule). These subjects will receive 1 dose of the MenACWY vaccine at Day 211^.
- rMenB_0_6 group: subjects receiving 2 doses of rMenB+OMV NZ vaccine at Day 1 and Day 181 and one dose of placebo at Day 61 (0-,6-M schedule). These subjects will receive 1 dose of the MenACWY vaccine at Day 211^.
- Control group: subjects receiving 2 doses of placebo at Day 1 and Day 61 and 1 dose of MenACWY vaccine at Day 181. These subjects will receive 1 dose of placebo at Day 211^.

  * rMenB_0_2_6 group will also be evaluated for objectives pertaining to 0-,2-M vaccination schedule (rMenB+OMV NZ at Day 1 and Day 61).

  ^In order to let the subjects in rMenB_0_2_6 and rMenB_0_6 groups receive a dose of MenACWY vaccine in line with ACIP recommendations, the subjects in these groups will receive a vaccination of MenACWY on Day 211 (Visit 5) after completion of the post-vaccination 2 blood sampling. To maintain the blinding of the

study, subjects in the Control Group will receive a dose of Placebo. At this time point, the vaccine/ product is considered a non-study vaccine, and these are not associated with any study objectives/ endpoints. The Sponsor is responsible for the ongoing safety evaluation of the clinical trial subjects including events related to non-study vaccines.

Duration of the study: The study duration is approximately 18 months for each subject.

- **Epoch 001:** Starting at Visit 1 (Day 1) and ending at the post-vaccination 3 blood sampling visit (Visit 5; Day 211).
- **Epoch 002:** Starting after post-vaccination 3 blood sampling visit (Visit 5; Day 211) and ending at SFU 10 (T10; 360 days post-vaccination 3; Day 541).

Primary completion Date (PCD): Visit 5 (Day 211).

End of Study (EoS): The date of release of the last testing results, to be achieved not later than 8 months after Last Subject Last Visit (LSLV). If the completion of testing occurs prior the completion of the LSLV the latter date defines the end of study visit.

Study groups:

Table 2 Study groups, treatment and epochs foreseen in the study

Study Groups	Number of subjects	Age (Min-Max)	Treatment name	Vaccine/Product name	Epochs	
					Epoch 001 (Observer-blind)	**Epoch 002** (Observer-blind)
rMenB_0_2_6	150	10 – 25 y	Bexsero (Injection)	rMenB+OMV NZ	X	
			Menveo (Injection)	MenACWY		
rMenB_0_6	150	10 – 25 y	Bexsero (Injection)	rMenB+OMV NZ	X	
			Placebo (Injection)	NaCl		
			Menveo (Injection)	MenACWY		
Control	150	10 – 25 y	Placebo (Injection)	NaCl	X	
			Menveo (Injection)	MenACWY		

Table 3 Overview of study design: vaccination and blood draw schedule

Visits **Study Day**	**Visit 1** **Day 1**	**Visit 2** **Day 61**	**Visit 3** **Day 91**	**Visit 4** **Day 181**	**Visit 5** **Day 211**
Group **rMenB_0_2_6** **N=150**	Pre-vacc Blood sample rMenB+OMV NZ	rMenB+OMV NZ	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample MenACWY
Group **rMenB_0_6** **N=150**	Pre-vacc Blood sample rMenB+OMV NZ	Placebo	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample MenACWY
Group **Control** **N=150**	Pre-vacc Blood sample Placebo	Placebo	Post-vacc 2 Blood sample	MenACWY	Post-vacc 3 Blood sample Placebo

N = number of subjects; Pre-vacc = pre-vaccination; post-vacc = post-vaccination

Control: Placebo control.

Vaccination schedule: Day 1 (Visit 1), Day 61 (Visit 2) and Day 181 (Visit 4). In addition, a vaccination is planned on Day 211 (Visit 5) after post-vaccination 3 blood draw is done (Refer Table 3).

Treatment allocation: At Day 1, prior to the study vaccination, subjects will be randomized to 1 of the 3 study groups according to a 1:1:1 ratio.

Blinding: Observer-blind. Kindly refer to Protocol Amendment 1 (23MAY2019) Section 7.3 for details on blinding and unblinding procedures.

Sampling schedule:

- A total of 3 blood samples will be collected from each subject at Day 1 (pre-vaccination blood sample; approximately 10 mL), at Day 91 (post-vaccination 2 blood sample; approximately 25 mL) and at Day 211 (post-vaccination 3 blood sample; approximately 25 mL).
- Urine sampling: Urine samples for pregnancy testing will be collected from female subjects of child-bearing potential at Visit 1, Visit 2, Visit 4 and Visit 5, prior to the vaccination.

Data collection: Standardised electronic Case Report Form (eCRF). Solicited symptoms will be collected using a subject Diary (electronic Diary [eDiary]).

Safety follow-up: Regular safety follow-up will be done through telephone calls (T). There will also be an extended safety follow-up (ESFU) phone call 12 months post-vaccination 3 (Day 181; Visit 4). This ESFU phone call will also mark the study conclusion. Refer to Protocol Amendment 1 23MAY2019 Table 6 and Section 8.5.3 for details on the safety follow-up.

4. ANALYSIS SETS

4.1. Definition

4.1.1. All Enrolled Set

All subjects who sign informed consent.

4.1.2. Exposed Set

All subjects who received at least 1 dose of the study treatment. The allocation in a group is done in function of all administered treatments.

4.1.3. Full Analysis Set (FAS), Effectiveness/Immunogenicity Set

4.1.3.1. FAS effectiveness (Month 3)

All subjects in the All Enrolled Set who:

- are randomized;
- receive a study vaccination; and
- provide evaluable serum sample with enc-hSBA result for the endemic *N. meningitidis* serogroup B invasive disease strain at Month 3 (Day 91/Visit 3).

4.1.3.2. FAS effectiveness (Month 7)

All subjects in the All Enrolled Set who:

- are randomized;
- receive a study vaccination; and
- provide evaluable serum sample with enc-hSBA result for the endemic *N. meningitidis* serogroup B invasive disease strain at Month 7 (Day 211/Visit 5).

4.1.3.3. FAS immunogenicity (Month 3)

All subjects in the All Enrolled Set who:

- are randomized;
- receive a study vaccination; and
- provide evaluable serum sample with hSBA result for at least one of the four *N. meningitidis* serogroup B indicator strains at Month 3 (Day 91/ Visit 3).

To assess the GMRs and the percentages of subjects with four-fold rise in hSBA titer, lab results of the subjects from FAS immunogenicity (Month 3) whose hSBA titer is also available at baseline (Day 1/Visit 1) will be analysed.

4.1.3.4. FAS immunogenicity (Month 7)

All subjects in the All Enrolled Set who:

- are randomized;
- receive a study vaccination; and
- provide evaluable serum sample with hSBA result for at least one of the four *N. meningitidis* serogroup B indicator strains at Month 7 (Day 211/ Visit *5*).

To assess the GMRs and the percentages of subjects with four-fold rise in hSBA titer, lab results of the subjects from FAS immunogenicity (Month 7) whose hSBA is also available at baseline (Day 1/ Visit 1) will be analysed.

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

4.1.4. Per Protocol Set (PPS), Effectiveness/Immunogenicity Set

4.1.4.1. PPS effectiveness (Month 3)

All subjects in the FAS effectiveness (Month 3) who:

- Correctly receive the study vaccine (i.e., receive the vaccine to which the subjects were randomized).
- Have no reportable protocol deviation as defined for period prior to Month 3 (Day 91/Visit 3) prior to unblinding or analysis.

4.1.4.2. PPS effectiveness (Month 7)

All subjects in the FAS effectiveness (Month 7) who:

- Correctly receive the study vaccine (i.e., receive the vaccine to which the subjects were randomized).
- Have no reportable protocol deviation as defined for period prior to Month 7 (Day 211/Visit 5) prior to unblinding or analysis.

In case of vaccination error, the subject is excluded from the PPS. If a subject receives a vaccine, labeled for another subject but the same as the one the subject was randomized to, the subject will not be removed from the PPS.

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

If a subject is unblinded during the study, except for SUSAR, he/she will be excluded from the PPS.

4.1.5. Safety Set

4.1.5.1. Solicited Safety Set

All subjects who received at least 1 dose of the study treatment (Exposed Set).

4.1.5.2. Unsolicited Safety Set

All subjects who received at least 1 dose of the study treatment (Exposed Set) that report unsolicited AEs/report not having unsolicited AEs.

4.1.5.3. Overall Safety Set

All subjects that belong to the Unsolicited safety or/and to the Solicited safety set.

For analyses of the safety endpoints, subjects will be analyzed “as treated” according to the actual vaccination a subject received.

4.1.6. Other Analysis Set

No other analysis sets are defined.

4.2. Criteria for eliminating data from Analysis Sets

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

4.2.1. Elimination from Exposed Set (ES)

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

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

4.2.2.1. Excluded subjects

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

Table 4 Elimination code and condition to exclude a subject from the PPS analysis

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
800	Fraudulent data	All	All
900	Invalid informed consent	All	All
1030	Study vaccine not administered at all	All	All
1050	Randomization failure	Visit 1, 2, 4	Effectiveness M3, and M7,

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
			Immunogenecity M3 and M7
1060	Randomization code was broken	All	Effectiveness M3, and M7, Immunogenecity M3 and M7
1070	Subjects got vaccinated with the correct vaccine but containing a lower volume	Visit 1, 2	Effectiveness M3, and M7, Immunogenecity M3 and M7
1070	Subjects got vaccinated with the correct vaccine but containing a lower volume	Visit 4	Effectiveness M7, Immunogenecity M7
1070	Vaccination not according to protocol	Visit 1, 2	Effectiveness M3, and M7, Immunogenecity M3 and M7
1070	Vaccination not according to protocol	Visit 4	Effectiveness M7, Immunogenecity M7
1080	Vaccine temperature deviation	Visit 1, 2	Effectiveness M3, and M7, Immunogenecity M3 and M7
1080	Vaccine temperature deviation	Visit 4	Effectiveness M7, Immunogenecity M7
1090	Expired vaccine administered	Visit 1, 2	Effectiveness M3, and M7, Immunogenecity M3 and M7
1090	Expired vaccine administered	Visit 4	Effectiveness M7, Immunogenecity M7
1500	Other deviation from study procedures not able to classified under any other categories	All	All
1500	Any other GCP non-compliance not able to classified under any other categories	All	All
2010	Protocol violation (inclusion/exclusion criteria)	All	Effectiveness M3, and M7, Immunogenecity M3 and M7

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
2040	Administration of any medication forbidden by the protocol	Visit 1, 2, 3 (before BS2)	Effectiveness M3, and M7, Immunogenecity M3 and M7
2040	Administration of any medication forbidden by the protocol	Visit 3 (after BS 2), 4, 5 (before BS3)	Effectiveness M7, Immunogenecity M7
2050	Not withdrawn after developing withdrawal criteria other than prohibited concomitant vaccination/medication (medical condition forbidden)	All	Effectiveness M3, and M7, Immunogenecity M3 and M7
2060	Concomitant infection related to the vaccine which may influence immune response (only meningococcal infection)	All	Effectiveness M3, and M7, Immunogenecity M3 and M7
2080	Subjects did not comply with vaccination schedule	Visit 1, 2	Effectiveness M3, and M7, Immunogenecity M3 and M7
2080	Subjects did not comply with vaccination schedule	Visit 4	Effectiveness M7, Immunogenecity M7
2090	Subjects did not comply with blood sample schedule	Visit 3	Effectiveness M3, Immunogenecity M3
2090	Subjects did not comply with blood sample schedule	Visit 5	Effectiveness M7, Immunogenecity M7
2100	Serological results not available post-vaccination for any of the endemic *N. meningitidis* serogroup B invasive disease strains	Visit 3	Effectiveness M3
2100	Serological results not available post-vaccination for any of the endemic *N. meningitidis* serogroup B invasive disease strains	Visit 5	Effectiveness M7
2100	Serological results not available post-vaccination for any of the four *N. meningitidis* serogroup B indicator strains	Visit 3	Immunogenecity M3
2100	Serological results not available post-vaccination for any of the four	Visit 5	Immunogenecity M7

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
	N. meningitidis serogroup B indicator strains		
2120	Obvious incoherence or abnormality or error in data related to testing of the endemic *N. meningitidis* serogroup B invasive disease strains	Visit 3	Effectiveness M3
2120	Obvious incoherence or abnormality or error in data related to testing of the endemic *N. meningitidis* serogroup B invasive disease strains	Visit 5	Effectiveness M7
2120	Obvious incoherence or abnormality or error in data related to testing of the four *N. meningitidis* serogroup B indicator strains	Visit 3	Immunogenecity M3
2120	Obvious incoherence or abnormality or error in data related to testing of the four *N. meningitidis* serogroup B indicator strains	Visit 5	Immunogenecity M7
2130	Biological sample specimen procedures not compliant with protocol	Visit 3	Effectiveness M3, Immunogenecity M3
2130	Biological sample specimen procedures not compliant with protocol	Visit 5	Effectiveness M7, Immunogenecity M7

4.2.3. Elimination from unsolicited and solicited safety set

4.2.3.1. Excluded subjects

4.2.3.1.1. Unsolicited safety set

Code 1030 (Study vaccine not administered at all), code 800 (fraudulent data), code 900 (invalid informed consent) and code 2150 (no post-vaccination unsolicited safety data) will be used for identifying subjects eliminated from the unsolicited safety set.

4.2.3.1.2. Solicited safety set

Code 1030 (Study vaccine not administered at all), code 800 (fraudulent data), code 900 (invalid informed consent) and code 2160 (no post-vaccination solicited safety data) will be used for identifying subjects eliminated from the solicited safety set.

5. STATISTICAL ANALYSES

That standard data derivation rules and stat methods are described in section 10.1 while the study specific data derivation rules and stat methods are described in section 9.

5.1. Demography

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

Descriptive statistics (mean, standard deviation (SD), median, minimum and maximum) for age, height and weight and body mass index (BMI) at enrolment will be calculated overall and by vaccine group.

Distributions of subjects by sex, race, ethnic origin and geographic region will be summarized overall and by vaccine group.

5.1.2. Additional considerations

Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

5.2. Exposure

5.2.1. Analysis of exposure planned in the protocol

Distribution of subjects by vaccinations will be summarized by vaccine group for the Enrolled Set. In case of vaccination error, subjects will be analyzed “as treated” (according to the vaccine the subject actually received).

5.2.2. Additional considerations

Not applicable.

5.3. Effectiveness

5.3.1. Analysis of effectiveness planned in the protocol

Primary:

Statistical Hypotheses: H_0: Vaccine Effectiveness (VE) ≤ 40% vs. H_1: Vaccine Effectiveness (VE) > 40%

Analysis set: FAS effectiveness is the primary analysis population with the findings repeated for PPS effectiveness as a sensitivity analysis.

Statistical method: The VE for 110 strains combined will be analyzed using a generalized linear model with vaccine group, strain and center as independent variables.

A center effect will be tentatively included in the analysis; if the statistical model does not converge due to the factor "center", a model without center effect will be fitted instead. The response variable of the model will be the Bernoulli distributed outcome of not killed at a 1:4 dilution (i.e. response is 1 if titer < 4, and 0 if titer ≥ 4). For the statistical analysis it is assumed that the response to each strain is an independent measure with a unique true underlying rate and VEs are expected to vary among the strains.

In order to obtain the VE measure which is a measure based on the relative risk (RR), PROC GENMOD will be used with the Poisson distribution and log link options in order to compute the log10 RR and the corresponding 95% CI. These values will be exponentiated to obtain the RR and the corresponding 95% CI. The VE will be computed as 100 x (1 – RR). If the lower limit of the 95% CI for VE is > 40% the null hypothesis will be rejected and effectiveness will be claimed. Additionally, in the event that the lower limit of the 95% CI for VE is > v% (v>40), a VE of v% will be claimed.

Since there are 3 primary endpoints, type I error adjustment is needed by controlling the global α at the level of 0.05. A gate-keeping testing strategy will be used. Testing with full α at 0.05 will begin with the endpoint with the 0-,2-,6-M schedule. If the testing is successful, full α will be propagated to the testing of the 2nd primary endpoint with the 0,6 months schedule. Finally, full α will be further propagated to the 3rd primary endpoint with the 0,2 months schedule if the 2nd primary endpoint is successfully tested.

Effectiveness criteria: Effectiveness of rMenB+OMV NZ vaccine will be demonstrated if the lower limit of the two-sided 95% CI for vaccine effectiveness against a selected strain panel between the rMenB+OMV NZ and the MenACWY group is above 40%.

Success criteria: The study is considered a success if the **criterion to demonstrate effectiveness is met for at least one of the vaccination schedules.**

Secondary:

Statistical Hypotheses: Not applicable

Analysis set: FAS Effectiveness is the primary analysis population.

Statistical method: The VE for each strain is defined as [1 – (percentage of subjects without bactericidal serum activity using enc-hSBA in rMenB+OMV NZ / percentage of subjects without bactericidal serum activity using enc-hSBA in MenACWY group)] x 100. VE against each of the selected endemic US *N. meningitidis* serogroup B strains will be evaluated by calculation of the point estimate for the relative risk (VE = [1-RR] x 100) and corresponding 95% CI.

The distribution of subjects by percentages of US N.menigitidis serogroup B invasive disease strains killed using enc-hSBA in each subject and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method [Clopper, 1934] will be calculated for each vaccine group at baseline at Day 91 (one month after the 2- dose vaccination series) and at Day 211 (one month after the 3-dose vaccination series).

The percentages of subjects whose sera kill ≥70% of the tested strains and 95% Clopper Pearson CIs will be calculated.

5.3.2. Additional considerations

1. The SAS codes to analyse the primary effectiveness objective is specified below. Treatment, center, and strains will be modelled as fixed effect. In order to account for a possible over-dispersion, the DSCALE option in the model statement will be evaluated first. The DSCALE will be kept in the model only if the F-statistics for the DSCALE parameter is significant (p<0.05). The following SAS code will be used for the VE calculation:

```
ods trace on;
ods output  PARAMETERESTIMATES = genmod_stats
            LSMEANS = lsmeans
            CONVERGENCESTATUS = converge ;

PROC GENMOD data=dataset descending;
   class trtgrp strain /*center*/;
   model s = trtgrp strain /*center*/ / dist=poi link=log DSCALE;
   lsmeans trtgrp strain /*center*/ / CL ILINK ;
run;

ods output close;

data genmod_stats;
   set genmod_stats;
   where parameter = 'trtgrp' and level1 = 'MenB';
   rr = exp(estimate);
   ub = exp(upperwaldcl);
   ul = exp(lowerwaldcl);
   ve = (1 - rr)*100 ;
   ve_low = (1 - ub) * 100 ;
   if ve_low > 40 then success = 1 ;
                  else success = 0 ;
run;
```

   where s represents the Bernoulli outcome measure (1 if titer < 4 or 0 if titer ≥ 4), trtgrp (MenB or MenACWY) indicates the vaccine group, MenB has 3 levels, corresponding to the 3 vaccination series defined in the primary endpoints (rMenB_0_2_6, rMenB_0_2, rMenB_0_6), strain is the serogroup B strain variable, and center is the site.

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

   rr is the relative risk (RR), which is obtained from the estimated parameters from PROC GENMOD. Vaccine effectiveness(VE) is then derived as (1-rr)x100%.

   ub and ul represents the lower and upper 95% CL of the relative risk. ve_low is the lower 95% CL of VE, if the value is greater than 40%, then the primary effectiveness objective is claimed successful.

2. Analyses of the primary objective will be repeated by age group (10-17 years of age and 18-25 years of age), race and sex.

3. A sensitivity analysis of the primary effectiveness endpoint for FAS effectiveness analysis populations may be performed using poisson regression, treatment and center are to be modelled as fixed effect, while strain is modelled as random. Below is an example of the SAS code for VE calculation:

```
ods trace on;
ods output  PARAMETERESTIMATES = genmod_stats
            LSMEANS = lsmeans
            CONVERGENCESTATUS = converge ;

PROC GENMOD data=dataset descending;
      class trtgrp strain /*center*/;
      model s = trtgrp /*center*/ / dist=POI link=log DSCALE;
      repeated subject = strain / type = US PRINTMLE ;
      lsmeans trtgrp strain /*center*/ / CL ILINK ;
run;

data genmod_stats; set genmod_stats;
      where parameter = 'trtgrp' and level1 = 'MenB';
      rr = exp(estimate);
      ub = exp(upperwaldcl);
      ul = exp(lowerwaldcl);
      ve = (1 - rr)*100 ;
      ve_low = (1 - ub) * 100 ;
      if ve_low > 40 then success = 1 ;
                     else success = 0 ;
run;
```

where s represents the Bernoulli outcome measure (1 if titer < 4 or 0 if titer ≥ 4), trtgrp (MenB or MenACWY) indicates the vaccine group, MenB has 3 levels, corresponding to the 3 vaccination series defined in the primary endpoints (rMenB_0_2_6, rMenB_0_2, rMenB_0_6), strain is the serogroup B strain variable, and center is the site.

rr is the relative risk (RR), which is obtained from the estimated parameters from PROC GENMOD. Vaccine effectiveness(VE) is then derived as (1-rr)x100%.

ub and ul represents the lower and upper 95% CL of the relative risk. ve_low is the lower 95% CL of VE, if the value is greater than 40%, then the primary effectiveness objective is claimed successful.

4. For the secondary effectiveness endpoint where VE of each individual strain is evaluated, the VE and the corresponding CI will be computed using the generalized linear model as described for the primary effectiveness endpoint. Except that each individual strain data will be analysed separately with treatment group and center as fixed variable in the model. However, in case of convergence issue the following hierarchical decision tree will be applied:

   - Poisson regression including center effect
   - Poisson regression, excluding center effect
   - Cochran-Mantel-Haenszel (CMH) method (if strain has 100% killed or 0% killed for ANY treatment)
   - VE set to 0% (if strain has 100% killed for both treatment)

5.4. Immunogenicity

5.4.1. Analysis of immunogenicity planned in the protocol

The analysis will be based on the FAS for the secondary immunogenicity objectives.

- The percentages of subjects with hSBA titers ≥ LLOQ for each of the M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA) and M07-0241084 (NHBA) test strains at one month after the 2-dose (0-,2-M; 0-,6-M) and 3-dose (0-,2-,6-M) vaccination series.
- The percentage of subjects with fourfold increase in hSBA titers relative to baseline for each of the M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA) and M07-0241084 (NHBA) test strains at one month after the 2-dose (0-,2-M; 0-,6-M) and 3-dose (0-,2-,6-M) vaccination series.
- GMTs and within group GMRs (relative to baseline) for each of the M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA) and M07-0241084 (NHBA) test strains at one month after the 2-dose (0-,2-M; 0-,6-M) and 3-dose (0-,2-,6-M) vaccination series.

5.4.2. Additional considerations

1. For each *N. meningitidis* serogroup B test strain (M14459, M07-0241084, 96217 and NZ98/254), the percentage of subjects with hSBA titers ≥ lower limit of quantitation (LLOQ) and the corresponding exact two-sided 95% CIs based on Clopper-Pearson method [Clopper, 1934] for each study group at baseline and at one month after the 2-dose (0-,2-M; 0-,6-M) and 3-dose (0-,2-,6-M) vaccination series. The CIs for the rate difference will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

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

2. For each *N. meningitidis* serogroup B test strain (M14459, M07-0241084, 96217 and NZ98/254), the percentages of subjects with fourfold increase in hSBA titers, and the corresponding exact two-sided 95% CIs based on the Clopper-Pearson method [Clopper, 1934] against these strains will be calculated for each study group at one months after the 2-dose (0-,2-M; 0-,6-M) and 3-dose (0-,2-,6-M) vaccination series. The CIs for the rate difference will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

   The percentage of subjects with fourfold increase in hSBA titers one month after the 2-dose (0-,2-M; 0-,6-M) and 3-dose (0-,2-,6-M) vaccination series relative to baseline defined as:

   - If the baseline titer is <limit of detection (LOD), then post-vaccination titer should be ≥ 4x LOD or ≥LLOQ, whichever is greater
   - If the baseline titer is ≥LOD but <LLOQ, then post-vaccination titer should be ≥4x LLOQ
   - If the baseline titer is ≥LLOQ, then post-vaccination titer should be ≥ 4x the baseline titer

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

3. The LLOQ and LOD for each *N. meningitidis* serogroup B test strain (M14459, M07-0241084, 96217 and NZ98/254) are shown in Table 5 below:

Table 5 LOD and LLOQ for the *N. meningitidis* serogroup B test strains

Strain	LOD	4*LOD	LLOQ
M14459	CCI		
96217			
NZ98/254			
M07-0241084			

4. In addition, a reverse cumulative distribution plot of each measure will be created.

5. The hSBA titers at each blood draw visit for each study group will be logarithmically transformed (base10) to fulfill the normal distribution assumption. For each *N. meningitidis* serogroup B test strain (M14459, M07-0241084, 96217 and NZ98/254), the GMTs and GMRs (one month after 2-dose / baseline, one month after 3-dose / baseline) will be calculated, with their associated two-sided 95% CIs, by exponentiating the corresponding log-transformed means and within-subject mean difference, respectively and their 95% CIs.

   The ratio of GMTs and GMRs between the Control group and the rMenB+OMV NZ group (0-,2-M, 0-,6-M, or 0-,2-,6-M vaccination series), and the corresponding CI will be constructed by exponentiating the mean difference and the confidence limits in log10 (titer), using ANOVA with study center included as an independent variable.

   Summary tables will show adjusted GMTs and GMRs and adjusted ratios of GMTs and GMRs for each vaccine group. To incorporate possible baseline imbalance among the vaccine groups, an analysis of covariance (ANCOVA) might be performed as sensitivity analysis that incorporate baseline titers along with study group and center as factors in the model.

   The following SAS code will be used for the ANOVA model:

```
PROC GLM data = dataset;
     class trtgrp center;
     model Ab_post = trtgrp center;
     lsmeans trtgrp / stderr cl tdiff pdiff;
     estimate 'Group A vs. Group B' trtgrp 1 -1;
run;
```

   where Ab_post represents the log-transformed antibody value of the immunogenicity variable at a given post baseline timepoint, trtgrp indicates the vaccine group, and center is the site.

The following SAS code will be used for the ANCOVA model:

```
PROC GLM data = dataset ;
     class trtgrp center Ab_pre ;
     model Ab_post = trtgrp center Ab_pre ;
     lsmeans trtgrp / stderr cl tdiff pdiff ;
     estimate 'Group A vs. Group B' trtgrp 1 -1 ;
run;
```

where Ab_post represents the log-transformed antibody value of the immunogenicity variable at a given post baseline timepoint, trtgrp indicates the vaccine group, center is the site, and Ab_pre is the log-transformed antibody baseline value of the immunogenicity variable.

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

5.5. Analysis of safety and reactogenicity

5.5.1. Analysis of safety and reactogenicity planned in the protocol

5.5.1.1. Analysis of Solicited Adverse events

Endpoints description: The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) adverse events during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181.

All solicited adverse events will be summarized according to defined severity grading scales, see protocol section 12.5.9.3.

Frequencies and percentages of subjects experiencing each adverse event will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic adverse event overall and at each time point will also be presented.

Post-vaccination solicited adverse events reported from Day 1 to Day 7 will be summarized for the intervals Day 1-3, Day 4-7, and Day 1-7 by maximal severity and by vaccine group, excluding the 30-minute measurement, which will be summarized separately. The severity of solicited local adverse 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 (1 to 24mm); Mild (25 to 50mm); Moderate (51 to 100mm); Severe (>100mm).

Injection site tenderness and systemic reactions (except fever) occurring up to 7 days after each vaccination at Day 1, Day 61 and Day 181 will be summarized according to “mild”, “moderate” or “severe”.

Each solicited local and systemic adverse event will also be further summarized as “none” versus “any” (for fever the latter will be ≥38.0 °C).

Implausible measurements (for further definition see eDiary specification) will be left out of the analysis.

Use of antipyretics and analgesics will be summarized by frequency by type of use (prophylactic versus treatment) and percentage of subjects 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 temperatures ≥ 38.0 °C and temperatures ≥ 40.0 °C will also be presented.

5.5.1.2. Analysis of Unsolicited Adverse events

Endpoints description: The frequencies and percentages of subjects with any unsolicited AEs (including all SAEs), AEs leading to withdrawal and medically attended AEs during the 7 and the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181.

The frequencies and percentages of subjects with SAEs, AEs leading to withdrawal and medically attended AEs throughout the study period.

This analysis applies to all adverse events occurring during the study, judged either as probably related, possibly related, or not related to vaccination by the investigator, recorded in AE CRF, with a start date on or after the date of first vaccination. AE starting prior to the first vaccination will only be listed. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class.

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

Separate summaries will be produced for the following categories:

- Serious adverse events.
- Adverse events that are possibly or probably related to vaccine.
- Adverse events of special interest.
- Adverse event leading to withdrawal.
- Adverse events leading to a medically attended visit.
- Adverse event by data source.

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

Local and systemic AEs will be analyzed by point estimates with associated 95% CIs [Clopper, 1934].

5.5.2. Additional considerations

5.5.2.1. Clarification for the Definition of Solicited Safety Set

All subjects who received at least 1 dose of the study treatment (Exposed Set) who have solicited safety data beyond 30-minute measurement up to day 7.

5.5.2.2. Clarification for the Analysis of Unsolicited Adverse Events

Summary of AE by data source described in study protocol will not be performed since this AE category is no longer captured during study.

The AEs that are possibly or probably related to vaccine are rephrased as AEs that are related to vaccine.

5.5.2.3. Combined Solicited and Unsolicited Adverse Events

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.

5.5.2.4. Concomitant Medication

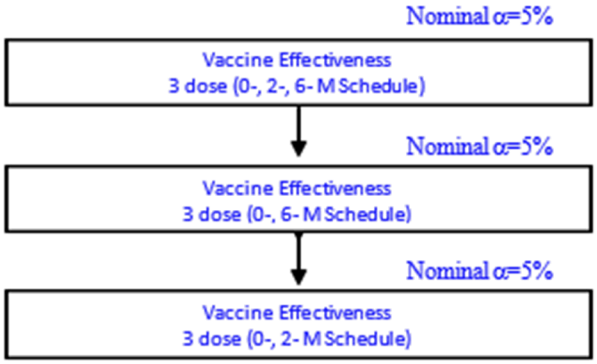
Medications will be coded using the GSKDRUG dictionary. The frequencies and percentages of subjects starting concomitant medications during 30 days post vaccination will be tabulated by vaccine group.

6. ANALYSIS INTERPRETATION

The primary endpoint is composed of 3 primary endpoints, type I error adjustment is needed by controlling the global α at the level of 0.05. A serial gate-keeping testing strategy will be used. Testing with full α at 0.05 will begin with the endpoint with the 0-,2-,6-M schedule. If the testing is successful, full α will be propagated to the testing of the 2nd primary endpoint with the 0,6 months schedule. Finally, full α will be further propagated to the 3rd primary endpoint with the 0,2 months schedule if the 2nd primary endpoint is successfully tested (see Figure 2)

Figure 2 Sequence for evaluating the study objectives in order to control the overall type I error below 5%

An objective will be reached if its associated criterion is met and the previous objectives were reached



7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

The final study report will contain at least the final analyses of all primary and secondary endpoints.

Description	Disclosure Purpose (CTRS=public posting, SR=study report, internal)
Final Analysis (Analysis_E1_01)	Public disclosure, Study report

7.2. Statistical considerations for interim analyses

Not applicable.

8. CHANGES FROM PLANNED ANALYSES

Not applicable.

9. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

The following sections describe additional derivation rules and statistical methods which are not presented in section 10.1.

9.1. Data derivation

Not applicable.

9.2. Statistical Method

Not applicable.

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

This section contains GSK Vaccines' standard rules for data display and derivation for clinical and epidemiological studies. These rules will be applied along with those detailed in section 9 (additional study-specific rules).

10.1.1. Attributing events to vaccine doses

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

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

10.1.2. Handling of missing data

10.1.2.1. Dates

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

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

The following exceptions apply:

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

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

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

10.1.2.2. Laboratory data

Missing laboratory results (including immunological data) will not be replaced.

10.1.2.3. Daily recording of solicited adverse events

10.1.2.3.1. Studies with electronic diaries

For studies using electronic diaries for the collection of solicited adverse events, a solicited adverse event will be considered present only when a daily recording of grade 1 or more is present.

10.1.2.3.2. Studies with paper diaries

For studies using paper diaries which have questions in the CRF indicating the presence or absence of solicited adverse events, the following rules are applicable.

Denominators for the summary of local (or general) solicited adverse events will be calculated using the number of subjects who respond "Yes" or "No" to the question concerning the occurrence of local (or general) adverse events.

When a specific solicited adverse event is marked as having not occurred following a specific vaccination (i.e. SDTM CE.CEOCCUR=N for the specified post-vaccination period for the adverse event in question), all daily measurements will be imputed as Grade 0.

When a specific solicited adverse event is marked as having occurred following a specific vaccination (i.e. SDTM CE.CEOCCUR=Y for the specified post-vaccination period for the adverse event in question), any missing daily recordings will be given imputed values to allow them to contribute to the 'Any' rows but not to specific grade rows of the solicited adverse event summary tables.

When the occurrence of a specific solicited adverse event is not present (i.e. SDTM CE.CEOCCUR is neither Y nor N for the specified post-vaccination period for the symptom in question) but the group of solicited adverse events (local or general) is marked as having occurred (i.e. SDTM CE.CEOCCUR=Y), all missing daily recordings

will be given imputed values to allow them to contribute to the 'Any' rows but not to specific grade rows of the solicited adverse event summary tables.

The following table shows how subjects contribute to each category for a specific solicited adverse event over the Day X to Day Y post-vaccination period:

Solicited adverse event category	Subjects included in the calculation of the numerator
Any	All subjects with at least one occurrence of the adverse event at grade 1, grade 2, or grade 3 between Day X and Day Y or with the adverse event marked as present and at least one missing daily recording between Day X and Day Y
At least grade 1	All subjects with at least one occurrence of the adverse event at grade 1, grade 2, or grade 3 between Day X and Day Y
At least grade 2	All subjects with at least one occurrence of the adverse event at grade 2 or grade 3 between Day X and Day Y
At least grade 3	All subjects with at least one occurrence of the adverse event at grade 3 between Day X and Day Y

10.1.2.4. Unsolicited adverse events

Unsolicited adverse event summaries are including serious adverse events unless specified otherwise.

Missing severity, relationship with study vaccine, and outcome of unsolicited adverse events will not be replaced and will appear as 'UNKNOWN' in all statistical output.

10.1.3. Data derivation

10.1.3.1. Age at vaccination in days

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

Age = date of vaccination minus date of birth

10.1.3.2. Age at vaccination in months

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

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

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

10.1.3.3. Age at vaccination in years

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

DOB = 10SEP1983, Date of vaccination = 09SEP2018 -> Age = 34 years

DOB = 10SEP1983, Date of vaccination = 10SEP2018 -> Age = 35 years

10.1.3.4. Weight

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

Weight in kilograms = Weight in pounds / 2.2

10.1.3.5. Height

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

Height in centimeters = Height in inches x 2.54

10.1.3.6. Body mass index (BMI)

BMI will be calculated as follows:

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

10.1.3.7. Temperature

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

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

10.1.3.8. Numerical serology results

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

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

10.1.3.9. Geometric mean titers (GMTs) and concentrations (GMCs)

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

10.1.3.10. Onset day

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

10.1.3.11. Duration of events

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

The duration of solicited events will be calculated as the sum of the individual days with the adverse event reported at grade 1 or higher during the solicited adverse event period.

10.1.3.12. Counting rules for combining solicited and unsolicited adverse events

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

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

10.1.3.13. Counting rules for occurrences of solicited adverse events

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

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with:

- no decimals when there are fewer than 50 subjects in each tabulated group
- one decimal when there are at least 50 subjects in at least one tabulated group

  Exceptions will be made for percentages that are not 0% or 100% but appear as 0% or 100% due to rounding. For these specific cases the number of decimals will be increased until the displayed value is no longer 0% or 100%. Examples are given in the following table.

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

  The display of additional decimals for values close to 0% or 100% will be applied only to point estimates and not confidence limits, which can be rounded and displayed as 0% or 100%.

  Values of exactly 0% or 100% will be presented with no decimals regardless of the number of subjects per tabulated group.

10.1.4.2. Differences in percentages

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

10.1.4.3. Demographic/baseline characteristics statistics

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

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

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

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

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

10.1.4.4. Serological summary statistics

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

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

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

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

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

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

10.1.5.2. Standardized asymptotic confidence intervals around differences in proportions

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

10.1.5.3. Adjusted GMT or GMC ratios

The CI for GMC ratio and adjusted GMT will be obtained using an ANOVA model on the logarithm transformed titers. The ANOVA model will include the vaccine group as the fixed effect (2 groups) and the center effect. The GMC ratio and their 95% CI will be derived by exponential transformation of the corresponding group contrast in the model.

10.2. TFL TOC

The Table Figure Listing (TFL) Table Of Contents (TOC) which itemizes the planned list of TFL and their associated lay-out is developed as a separate document.

11. REFERENCES

Clopper CJ, Pearson E. The Use of Confidence or Fiducial Limits Illustrated in the case of the Binomial. *Biometrika.* 1934;26:404-13.

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