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EMA/466192/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

MenQuadfi

Meningococcal Group A, C, W and Y conjugate vaccine

Procedure no: EMEA/H/C/005084/P46/013

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	22/07/2024	22/07/2024
☐	CHMP Rapporteur Assessment Report	26/08/2024	26/08/2024
☐	CHMP members comments	09/09/2024	09/09/2024
☐	Updated CHMP Rapporteur Assessment Report	12/09/2024	N/A
☒	CHMP adoption of conclusions:	19/09/2024	19/09/2024

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1. Introduction

On 03 July 2024, the MAH submitted a completed paediatric study for MenQuadfi, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study MET42 "Phase III, partially modified double-blind, randomized, parallel-group, active controlled, multi-center study to compare the immunogenicity and describe the safety of MenACYW conjugate vaccine and MENVEO (Meningococcal [Serogroups A, C, Y, and W-135] Oligosaccharide Diphtheria CRM197 Conjugate Vaccine) when administered concomitantly with routine pediatric vaccines to healthy infants and toddlers in the US" is part of a clinical development program. The variation application consisting of the full relevant data package (i.e. ongoing paediatric clinical studies covering 6 to 12 months population: MET33, MET41, MET42, MET52, MET58, MET61) is expected to be submitted in Q1 2025. A line listing of all the concerned studies is annexed.

MenQuadfi is currently indicated in the European Union (EU) from the age of 12 months and older against invasive meningococcal disease caused by Neisseria meningitidis serogroups A, C, W and Y.

2.2. Information on the pharmaceutical formulation used in the study

MenQuadfi is currently approved in the European Union (EU) for the active immunisation from the age of 12 months and older against invasive meningococcal disease caused by Neisseria meningitidis serogroups A, C, W and Y.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- **Study MET42**: An immunogenicity and safety study of a 4-dose immunization schedule of MenQuadfi (Meningococcal [Groups A, C, Y, and W-135] polysaccharide Tetanus Toxoid Conjugate Vaccine) or of MENVEO (Meningococcal [Groups A, C, Y, and W-135] Oligosaccharide Diphtheria CRM197 Conjugate Vaccine) when administered concomitantly with routine paediatric vaccines to healthy infants aged ≥ 42 to ≤ 89 days in the United States.

2.3.2. Clinical study MET42

Description

Study MET42 is a Phase III, partially modified double-blind, randomized, parallel-group, active controlled, multi-center study to compare the immunogenicity and describe the safety of MenACYW conjugate vaccine and MENVEO (Meningococcal [Serogroups A, C, Y, and W-135] Oligosaccharide Diphtheria CRM197 Conjugate Vaccine) when administered concomitantly with routine pediatric vaccines to healthy infants and toddlers in the US.

Table 1: Vaccination and blood sampling schedule

Age in months	2 months		4 months	6 months	7 months		12 months		13 months	15 months		16 months
Visit #	Visit 1		Visit 2	Visit 3	Visit 4		Visit 5*		Visit 6: 1a† and 2a	Visit 6: 1b and 2b Visit 7: 2a		Visit 7: 1b and 2b Visit 8: 2a
Group	Blood Draw‡	Vaccines	Vaccines	Vaccines	Blood Draw	Subgroup	Blood Draw‡	Vaccines	Blood Draw	Blood Draw‡	Vaccines	Blood Draw
1	X	MenACYW Pentacel PCV13 rotavirus hepatitis B§	MenACYW Pentacel PCV13 rotavirus	MenACYW Pentacel PCV13 rotavirus hepatitis B	X	1a	X	MenACYW MMR varicella PCV13	X	No study visit *Pentacel***		
						1b		MMR varicella PCV13	No study visit	X	MenACYW Pentacel Hepatitis A	X
2	X	MENVEO Pentacel PCV13 rotavirus hepatitis B§	MENVEO Pentacel PCV13 rotavirus	MENVEO Pentacel PCV13 rotavirus hepatitis B	X	2a	X	MENVEO MMR varicella PCV13	X		Pentacel Hepatitis A	
						2b		MENVEO MMR varicella PCV13	No study visit	X	Pentacel Hepatitis A	X

*Visit 5 occurred at 12 months of age for Subgroups 2a and 2b, and at 12 to 15 months of age for Subgroups 1a and 1b.
†Last study visit for Subgroup 1a. Routine vaccines could be administered as per standard of care after study procedures were completed. Visit 6 occurred at 13 to 16 months of age for Subgroup 1a. For Subgroup 2a, Visit 6 occurred at 13 months of age.
‡Blood was drawn prior to vaccinations.
§ The 1st dose of HB vaccine had to be received at least 28 days prior to the 1st study vaccination at Visit 1.
**Subjects in Subgroup 1a completed the last study visit at 13 to 16 months of age. Pentacel was provided by the Sponsor to complete the DTaP series with vaccine from the same manufacturer and had to be administered as per standard of care. The study personnel / Investigator was responsible for administering this dose at the recommended age outside of the scope of the study.

Methods

Study participants

The study population included healthy male and female subjects aged 42 to 89 days on the day of the first visit. Subjects had not been previously vaccinated against meningococcal disease with either mono- or polyvalent polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C, Y, or W, or meningococcal B serogroup vaccine, or any pneumococcal, diphtheria, tetanus, pertussis, poliomyelitis, hepatitis A, measles, mumps, rubella, varicella, Hib, and/or rotavirus vaccines. Subjects had to have received a first dose of hepatitis B vaccine at least 28 days prior to study enrollment.

Receipt of any vaccine in the 4 weeks preceding the first study vaccination (except for monovalent pandemic influenza vaccines and multivalent influenza vaccines, which could be received at least 2 weeks before or 2 weeks after any study vaccination), or planned participation in another clinical study investigating a vaccine, drug, medical device, or medical procedure at the time of enrollment or in the 4 weeks preceding the first study vaccination was not allowed.

Treatments

All subjects were randomised into two groups. Each group was further randomised in 2 subgroups based on the time of analyses conducted in the second year of life (30 days after the 12-month vaccinations or 30 days after the 15-month vaccinations, respectively):

Group 1 (G1): MenACYW conjugate vaccine and routine paediatric vaccines:

- **Subgroup 1a (G1a)** (12 months): MenACYW conjugate vaccine and routine vaccines at 2, 4, 6, and 12 to 15 months of age.
- **Subgroup 1b (G1b)** (15 months): MenACYW conjugate vaccine at 2, 4, 6, and 15 to 18 months of age and routine vaccines at 2, 4, 6, 12 to 15 months of age, and 15 to 18 months of age.

Group 2 (G2): MENVEO and routine paediatric vaccines

- **Subgroup 2a (G2a)** (12 months): MENVEO at 2, 4, 6, and 12 months of age and routine vaccines at 2, 4, 6, 12, and 15 to 18 months of age.
- **Subgroup 2b (G2b)** (15 months): MENVEO at 2, 4, 6, and 12 months of age and routine vaccines at 2, 4, 6, 12, and 15 to 18 months of age.

All subjects received the following routine vaccines as per the Advisory Committee on Immunization Practices (ACIP) recommendations:

• Pentacel (diphtheria-tetanus-acellular pertussis [DTaP]-inactivated poliovirus vaccine [IPV]/Hib) at 2, 4, 6, and 15 to 18 months of age (Subjects in Subgroup 1a completed the last study visit at 13 to 16 months of age. For subjects in Subgroup 1a, the fourth dose of Pentacel, which was administered at 15 to 18 months of age, had to be provided by the Sponsor for completion of the DTaP series with vaccine from the same manufacturer, as per ACIP recommendation. The study personnel / Investigator was responsible for administering this dose at the recommended age outside of the scope of the study.)

• PREVNAR 13 (PCV13) at 2, 4, 6, and 12 to 15 months of age.

• RotaTeq (pentavalent rotavirus vaccine [RV5]) at 2, 4, and 6 months of age.

• ENGERIX-B (HB vaccine) at 2 and 6 months of age (First dose of hepatitis B vaccine was to be given at least 28 days prior to study enrollment).

• M-M-R II (measles, mumps, rubella [MMR] vaccine) at 12 to 15 months of age.

• VARIVAX (varicella vaccine) at 12 to 15 months of age.

In addition, subjects in Subgroup 1b and Group 2 received the 1st dose of hepatitis A (HepA) vaccine (HAVRIX) at 15 to 18 months of age as part of the study. For Subgroup 1a, there was no HepA vaccination provided as part of the study. Subjects in Subgroup 1a had to be vaccinated, as per standard practice, after the completion of the last study visit.

Objectives

Primary Objectives:

1) To demonstrate the non-inferiority (NI) of the serum bactericidal assay using human complement (hSBA) vaccine seroresponse to meningococcal serogroups A, C, Y, and W following the administration of a 4-dose series of MenACYW conjugate vaccine compared to a 4-dose series of MENVEO when given concomitantly with routine paediatric vaccines to infants and toddlers 6 weeks old to 15 months old.

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

   - For a subject with a pre-vaccination titer < 1:8, the post-vaccination titer had to be ≥ 1:16
   - For a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer had to be ≥ 4-fold greater than the pre-vaccination titer

2) To demonstrate the NI of the hSBA antibody (Ab) response to meningococcal serogroups A, C, Y, and W following the administration of 3 doses in infancy of MenACYW conjugate vaccine compared to 3 doses in infancy of MENVEO when given concomitantly with routine paediatric vaccines to infants at 2, 4, and 6 months of age.

Secondary Objectives - *Immunogenicity*

1) To demonstrate the NI of immune responses of the routine paediatric vaccines administered concomitantly with MenACYW conjugate vaccine as compared with MENVEO in infants and toddlers 6 weeks old to 18 months old.

2) To assess the Ab responses against meningococcal serogroups A, C, Y, and W after the administration of the 4th dose of MenACYW conjugate vaccine or MENVEO when both were given concomitantly with routine paediatric vaccines at 12 months of age.

3) To assess the persistence of bactericidal Ab at 12 months of age in subjects who previously received 3 doses of MenACYW conjugate vaccine or MENVEO in infancy concomitantly with routine paediatric vaccines at 2, 4, and 6 months of age.

4) To describe the Ab responses against the antigens of the routine paediatric vaccines (Pentacel, PREVNAR 13, M-M-R II, VARIVAX, RotaTeq, and ENGERIX-B) when administered concomitantly with either MenACYW conjugate vaccine or MENVEO.

5) To describe the Ab responses against meningococcal serogroups A, C, Y, and W when MenACYW conjugate vaccine vs MENVEO was administered concomitantly with routine paediatric vaccines.

6) To describe the Ab responses against meningococcal serogroups A, C, Y, and W when MenACYW conjugate vaccine was administered to children 12 to 15 months of age vs when MenACYW conjugate vaccine was administered to children 15 to 18 months of age, concomitantly with routine pAediatric vaccines (Subgroup 1a vs Subgroup 1b), including the bactericidal antibodies persistence and the effect of 4th dose of MenACYW conjugate vaccine at 12 to 15 months of age or 15 to 18 months of age.

Observational Objectives - *Safety*

To describe the safety profile of MenACYW conjugate vaccine and MENVEO when administered concomitantly with routine paediatric vaccines in healthy infants and toddlers.

Outcomes/endpoints

Primary Endpoints

1) Meningococcal serogroups A, C, Y, and W Ab titers measured by hSBA before first study vaccination on Day (D) 0 and 30 days after the 4th meningococcal vaccination (Subgroup 1a versus (vs) Subgroup 2a).

2) Ab titers ≥ 1:8 against meningococcal serogroups A, C, Y, and W measured by hSBA assessed 30 days after vaccination(s) at 6 months of age (Group 1 vs Group 2).

Secondary Endpoints

Immunogenicity

1) The following serological endpoints were assessed:

• D0 (before 1st vaccination) for Group 1 and Group 2:

- Anti-rotavirus serum immunoglobulin (Ig) A Ab concentrations.

• 30 days after the 6-month vaccinations (after the 3rd dose) for Group 1 and Group 2:

- IgG Abs against hepatitis B (HB) surface antigen concentrations ≥ 10 milli international units (mIU)/mL.
- Anti polyribosyl-ribitol phosphate (PRP) Ab concentrations ≥ 0.15 μg/mL.
- Anti PRP Ab concentrations ≥ 1.0 μg/mL.
- Anti-poliovirus (types 1, 2, and 3) Ab titers ≥ 1:8.
- Anti-rotavirus serum IgA Ab concentrations with ≥ 3-fold rise over baseline.
- Anti-rotavirus serum IgA Ab geometric mean concentrations (GMCs).
- Anti-pertussis Ab concentrations (pertussis toxoid [PT], filamentous hemagglutinin adhesin [FHA], pertactin [PRN], and fimbriae 2 and 3 [FIM] GMCs).
- Anti-pneumococcal Ab concentrations (for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) (GMCs).

• 30 days after the 12-month vaccinations for Subgroup 1a and Subgroup 2a:

- Anti-measles Ab concentrations ≥ 255 mIU/mL.
- Anti-mumps Ab concentrations ≥ 10 mumps Ab units/mL.
- Anti-rubella Ab concentrations ≥ 10 IU/mL.
- Anti-varicella Ab concentrations ≥ 5 glycoprotein enzyme-linked immunosorbent assay (gpELISA) units/mL.
- Anti-pneumococcal Ab concentrations (for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) (GMCs).

• Before the 15-month vaccinations for Subgroup 1b and Subgroup 2b:

- Anti-pertussis Ab concentrations (PT, FHA, PRN, and FIM).

• 30 days after the 15-month vaccinations for Subgroup 1b and Subgroup 2b:

- Anti-PRP Ab concentrations ≥ 1.0 μg/mL.
- Anti-poliovirus (types 1, 2, and 3) Ab titers ≥ 1:8.
- Anti-pertussis Ab concentrations (PT, FHA, PRN, and FIM) (vaccine response).

Pertussis vaccine response definition:

- Pre-vaccination < lower limit of quantitation (LLOQ) then post-vaccination had to be ≥ 4x the LLOQ.
- Pre-vaccination > LLOQ but < 4x the LLOQ, then post-vaccination had to achieve a 4-fold rise (post- vaccination/pre-vaccination ≥ 4).
- Pre-vaccination > 4x the LLOQ, then post-vaccination had to achieve a 2-fold response (post-vaccination/pre-vaccination ≥ 2).

Subgroup analyses to examine consistency across study groups were performed and presented in the Statistical Analysis Plan (SAP).

2) The following serological endpoints were assessed (effect of 4th dose of MenACYW conjugate vaccine or MENVEO):

• Before the 12-month vaccinations (pre-4th dose) for Subgroups 1a and 2a:

- hSBA meningococcal serogroups A, C, Y and W Ab titers.

• 30 days after the 12-month vaccinations for Subgroups 1a and 2a:

- hSBA meningococcal serogroups A, C, Y and W Ab titers.
- hSBA meningococcal serogroups A, C, Y, and W Ab titers ≥ 4-fold rise from pre-4th dose (at 12 months of age) to post-dose 4 vaccination.

3) The following serological endpoints were assessed (persistence of bactericidal Abs after infant vaccination with MenACYW conjugate vaccine or MENVEO):

• 30 days after the 6-month vaccinations and before the 12-month vaccinations for Subgroup 1a and Subgroup 2a:

- hSBA meningococcal serogroups A, C, Y, and W Ab titers.
- hSBA meningococcal serogroups A, C, Y, and W Ab titers ≥ 1:4 and ≥ 1:8.

4) The following serological endpoints were assessed:

• Day 0 (before the 1st vaccination) for Groups 1 and 2:

- Anti-pertussis Ab concentrations (PT, FHA, PRN, FIM).

• 30 days after the 6-month vaccinations (after the 3rd dose) for Group 1 and Group 2:

- Anti-PRP Ab concentrations.
- Anti-diphtheria Ab concentrations.
- Anti-diphtheria Ab concentrations ≥ 0.01 IU/mL.
- Anti-diphtheria Ab concentrations ≥ 0.1 IU/mL.
- Anti-tetanus Ab concentrations.
- Anti-tetanus Ab concentrations ≥ 0.01 IU/mL.
- Anti-tetanus Ab concentrations ≥ 0.1 IU/mL.
- Anti-HBs Ab concentrations.
- Anti-HBs Ab concentrations ≥ 100 IU/mL.
- Anti-polio (types 1, 2, and 3) Ab titers.
- Anti-rotavirus serum IgA Ab concentrations.
- Anti-rotavirus serum IgA Ab concentrations with ≥ 4-fold rise over baseline.
- Anti-pertussis (PT, FHA, PRN, and FIM) Ab concentrations (vaccine response).
- Anti-pneumococcal Ab concentrations (pneumococcal 13-valent conjugate vaccine [PCV13]).
- Anti pneumococcal Ab concentrations (PCV13) ≥ 0.35 μg/mL.
- Anti-pneumococcal Ab concentrations (PCV13) ≥ 1 μg/mL.

• 30 days after the 12-month vaccinations for Subgroup 1a and Subgroup 2a:

- Anti-measles Ab concentrations.
- Anti-mumps Ab concentrations.
- Anti-rubella Ab concentrations.
- Anti-varicella Ab concentrations.
- Anti-pneumococcal Ab concentrations (PCV13).
- Anti-pneumococcal Ab concentrations (PCV13) ≥ 0.35 μg/mL.
- Anti-pneumococcal Ab concentrations (PCV13) ≥ 1 μg/mL.

• 30 days after the 6-month vaccinations and before vaccination at the 15-month vaccinations for Subgroup 1b and Subgroup 2b to evaluate immune persistence after primary series vaccination with *Haemophilus influenzae* type b (Hib) and pertussis vaccines:

- Anti-PRP Ab concentration ≥ 0.15 μg/mL.
- Anti-PRP Ab concentrations.
- Anti-pertussis (PT, FHA, PRN, and FIM) Ab concentrations.

• 30 days after the 15-month vaccinations for Subgroup 1b and Subgroup 2b:

- Anti-PRP Ab concentrations.
- Anti-diphtheria Ab concentrations.
- Anti-diphtheria Ab concentrations ≥ 0.1 IU/mL.
- Anti-diphtheria Ab concentrations ≥ 1.0 IU/mL.
- Anti-tetanus Ab concentrations.
- Anti-tetanus Ab concentrations ≥ 0.1 IU/mL.
- Anti-tetanus Ab concentrations ≥ 1.0 IU/mL.
- Anti-polio (types 1, 2, and 3) Ab titers.
- Anti-pertussis Ab concentrations (PT, FHA, PRN, and FIM) (GMCs).

5) The following serological endpoints were assessed:

• Day (D)0 (before 1st vaccination) for Group 1 and Group 2:

- hSBA meningococcal serogroups A, C, Y and W Ab titers.

• 30 days after the 6-month vaccinations (after the 3rd dose) for Group 1 and Group 2:

- hSBA meningococcal serogroups A, C, Y, and W Ab titers.
- Titer distribution and reverse cumulative distribution curves (RCDCs).
- hSBA meningococcal serogroups A, C, Y, and W Ab titers ≥ 1:4 and ≥ 1:8.
- hSBA meningococcal serogroups A, C, Y, and W Ab titers ≥ 4-fold rise from pre-vaccination (D0) to post-vaccination.
- hSBA vaccine seroresponse.

• Before the 12-month vaccinations for Subgroups 1a and 2a and before the 15-month vaccinations for Subgroup 1b:

- hSBA meningococcal serogroups A, C, Y and W Ab titers.

• 30 days after the 12-month vaccinations for Subgroups 1a and 2a and 30 days after the 15-month vaccinations for Subgroup 1b:

- hSBA meningococcal serogroups A, C, Y, and W Ab titers.
- Titer distribution and RCDCs.
- hSBA meningococcal serogroups A, C, Y, and W Ab titers ≥ 1:4 and ≥ 1:8.
- hSBA meningococcal serogroups A, C, Y, and W Ab titers ≥ 4-fold rise from pre-vaccination (D0) to post-dose 4 vaccination.
- hSBA vaccine seroresponse.

6) The following serological endpoints were assessed:

• D0 (before the 1st vaccination) for Subgroup 1a and Subgroup 1b:

- hSBA meningococcal serogroups A, C, Y and W Ab titers.

• 30 days after the 6-month vaccinations and before the 12-month vaccinations for Subgroup 1a and before the 15-month vaccinations for Subgroup 1b to evaluate the immune persistence after infant vaccination with MenACYW conjugate vaccine:

- hSBA meningococcal serogroups A, C, Y and W Ab titers.
- hSBA meningococcal serogroups A, C, Y, and W Ab titers ≥ 1:4 and ≥ 1:8.

• 30 days after the 12-month vaccinations for Subgroup 1a and 30 days after the 15-month vaccinations for Subgroup 1b, including evaluation of the effect of the 4th dose of MenACYW conjugate vaccine:

- hSBA meningococcal serogroups A, C, Y, and W Ab titers.
- hSBA meningococcal serogroups A, C, Y, and W Ab titers ratio (Subgroup 1b/Subgroup 1a).
- hSBA meningococcal serogroups A, C, Y, and W Ab titers ≥ 1:4 and ≥ 1:8.
- hSBA meningococcal serogroups A, C, Y, and W Ab titers ≥ 1:8 difference (Subgroup 1b - Subgroup 1a).
- hSBA meningococcal serogroups A, C, Y, and W Ab titers ≥ 4-fold rise from pre-vaccination (D0) to post-4th dose vaccination.
- hSBA meningococcal serogroups A, C, Y, and W Ab titers ≥ 4-fold rise from pre-4^{th} dose vaccination to post-4th dose vaccination.
- hSBA vaccine seroresponse.
- hSBA vaccine seroresponse difference (Subgroup 1b - Subgroup 1a).

Observational Endpoints - *Safety*

The following endpoints were used for all subjects for the evaluation of safety:

• Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, relationship to vaccination, and whether the event led to early termination

from the study, of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after each vaccination.

• Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and electronic case report book [CRB] injection site reactions occurring up to D07 after each vaccination.

• Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and CRB) systemic reactions occurring up to D07 after each vaccination.

• Occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to vaccination, and whether the event led to early termination from the study, of unsolicited AEs up to D30 after each vaccination.

• Occurrence, nature (MedDRA preferred term), time of onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the event led to early termination from the study, of serious AEs (SAEs) (including adverse events of special interest [AESIs]) throughout the trial from Visit 1 to the 6-month follow-up contact after the last vaccination.

• Occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to vaccination, and whether the event led to early termination from the study for medically attended adverse events (MAAEs) throughout the trial from Visit 1 to the 6-month follow-up contact after the last vaccination.

Sample size

Approximately 2628 subjects were planned to be enrolled. An estimated maximum of up to 34.1% non-evaluable subjects resulted in approximately 1732 subjects in the per-protocol analysis set (PPAS) available for immunogenicity analyses (1155 evaluable subjects in Group 1 and 577 in Group 2).

In case of unexpected situation or any study hold resulting in an unexpected number of unevaluable subjects, total sample size was to be increased to replace withdrawn, or unevaluable subjects.

Table 2: Study MET42 sample size

	Group 1: MenACYW Conjugate Vaccine + Routine Vaccines		Group 2: MENVEO + Routine Vaccines	
Subgroup	**1a**	**1b**	**2a**	**2b**
Planned	1752		876	
	1168	584	584	292
Actual	1746		881	
	1167	579	588	293
FAS1	1339		663	
FAS2	844	388	434	200
FAS3	816	378	398	193
PPAS1	928		460	
PPAS2	647	295	329	157
PPAS3	675	308	308	126
Overall SafAS	1727		867	
SafAS1	1727		867	
SafAS2	1620		827	
SafAS3	1542		794	
SafAS4	938	472	480	228
SafAS5	-	444	425	219
SafAS6	1375		705	

Abbreviations: FAS, Full Analysis Set, PPAS, Per-Protocol Analysis Set; SafAS, Safety Analysis Set

FAS subsets:

- FAS1 (for infant vaccination): subset of all randomized subjects who received ≥ 1 dose of the study vaccine in infancy (< 12 months of age) and had a valid post-vaccination serology result in infancy.
- FAS2 (for immunogenicity persistence evaluation): subset of all randomized subjects who received ≥ 1 dose of the study vaccine in infancy (at Visit 1 to 3, < 12 months of age) and had a valid pre-vaccination serology result at Visit 5 before the 12-month vaccinations for Subgroups 1a and 2a or at Visit 6 before the 15-month vaccinations for Subgroups 1b and 2b.
- FAS3 (for 2nd year of life vaccination): subset of all randomized subjects who received ≥ 1 dose of the study vaccine in the 2nd year of life (≥ 12 months of age) and had a valid post-vaccination serology result in the 2nd year of life.

PPAS subsets:

- PPAS1 (for infant vaccination): subset of FAS1 with no relevant protocol deviations during infancy.
- PPAS2 (for immunogenicity persistence evaluation): subset of FAS2 with valid pre-vaccination serology result at Visit 5 before the 12-month vaccination for Subgroups 1a and 2a or at Visit 6 before the 15-month vaccination for Subgroups 1b and 2b and with no relevant protocol deviations during infancy.
- PPAS3 (for 2nd year of life vaccination): subset of FAS3 with no relevant protocol deviations.

SafAS subsets:

- Overall SafAS: subjects who had received ≥ 1 dose of the study vaccines and had any safety data available.
- SafAS1 (vaccination at 2 months of age): subjects who had received the study vaccine at Visit 1 around 2 months of age and had any safety data available.
- SafAS2 (vaccination at 4 months of age): subjects who had received the study vaccine at Visit 2 around 4 months of age and had any safety data available.
- SafAS3 (vaccination at 6 months of age): subjects who had received the study vaccine at Visit 3 at around 6 months of age and had any safety data available.
- SafAS4 (vaccination at 12 months of age): subjects who had received the study vaccine at Visit 5 at around 12-15 months of age and had any safety data available.
- SafAS5 (vaccination at 15 months of age): subjects who had received the study vaccine at around 15-18 months of age and had any safety data available.
- SafAS6 (all 4-dose vaccination): subjects who had received all 4 doses of the study vaccine (3 doses in infancy and 1 dose in the 2nd year of life at 12 or 15 months of age) and had any safety data available.

For the primary objective 1 (after the 4th dose):

With 770 evaluable subjects in Subgroup 1a and 385 evaluable subjects in Subgroup 2a, the study had around 98.4% power by using the Farrington and Manning's method to declare the NI of Subgroup 1a vs Subgroup 2a.

For the primary objective 2 (after the 3rd dose):

With 1155 evaluable subjects in Group 1 and 577 evaluable subjects in Group 2, the study had around 98.8% power by using the Farrington and Manning's method to declare the NI of Group 1 vs Group 2.

Co-primary objectives:

The study had around 97.2% overall power by using the Farrington and Manning's method to declare the NI for co-primary objectives (Table 3).

Table 3: Power estimates to reject the primary hypotheses

Primary #	Antigen	Endpoint	Non-inferiority margin	Estimated response*	Power (%)
Primary 1 (4th dose)	A	Seroresponse Rate	10%	80%	98.4
	C	Seroresponse Rate	10%	90%	99.98
	Y	Seroresponse Rate	10%	90%	99.98
	W	Seroresponse Rate	10%	90%	99.98
Primary 2 (3rd dose)	A	% ≥ 1:8	10%	70%	99.2
	C	% ≥ 1:8	10%	80%	99.9
	Y	% ≥ 1:8	10%	80%	99.9
	W	% ≥ 1:8	10%	80%	99.9
	Overall				97.2

Evaluable subjects for Primary 1: Subgroup 1a: n=770 subjects; Subgroup 2a: n=385 subjects
Evaluable subjects for Primary 2: Group 1: n=1155 subjects; Group 2: n=577 subjects
*Estimated responses were based on results observed in MENVEO V59_33 (NCT01000311) and in study MET39 (Group 1 TetraMen-T 2, 4, 6, 12 months).

For the secondary objectives:

I. First year evaluation at 30 days after the 6-month vaccinations (after the 3rd dose)

With 1155 evaluable subjects in Group 1 and 577 evaluable subjects in Group 2, the study had around 94.2% power by using the Farrington and Manning' s method to declare the NI of Group 1 vs Group 2.

II. Second year evaluation at 30 days after the 12-month vaccinations

With 770 evaluable subjects in Subgroup 1a and 385 evaluable subjects in Subgroup 2a, the study had around >99.9% power by using the Farrington and Manning' s method to declare the NI of Subgroup 1a vs. Subgroup 2a.

III. Second year evaluation at 30 days after the 15-month vaccinations

With 385 evaluable subjects in Subgroup 1b and 192 evaluable subjects in Subgroup 2b, the study had around 98.6% power by using the Farrington and Manning' s method to declare the NI of Subgroup 1b vs Subgroup 2b.

Randomisation and blinding (masking)

Enrolled subjects were to be randomized 2:1 to the following 2 groups:

- **Group 1 (G1):** MenACYW conjugate vaccine and routine pediatric vaccines
- **Group 2 (G2):** MENVEO and routine pediatric vaccines

Each group was further randomized 2:1 in 2 subgroups based on the time of analyses conducted in the 2nd year of life (30 days after the 12-month vaccinations or 30 days after the 15-month vaccinations, respectively):

Group 1:

- **Subgroup 1a (G1a)** (12 months*): MenACYW conjugate vaccine and routine vaccines at 2, 4, 6, and 12 to 15 months of age

- **Subgroup 1b (G1b)** (15 months*): MenACYW conjugate vaccine at 2, 4, 6, and 15 to 18 months of age and routine vaccines at 2, 4, 6, 12 to 15 months of age, and 15 to 18 months of age

Group 2:

- **Subgroup 2a (G2a)** (12 months*): MENVEO at 2, 4, 6, and 12 months of age and routine vaccines at 2, 4, 6, 12, and 15 to 18 months of age

- **Subgroup 2b (G2b)** (15 months*): MENVEO at 2, 4, 6, and 12 months of age and routine vaccines at 2, 4, 6, 12, and 15 to 18 months of age

Statistical Methods

Primary objectives

Primary hypothesis 1 (seroresponse after the 4th dose)

Thirty days after the administration of the 4th dose of MenACYW conjugate vaccine at 12 to 15 months of age or MENVEO at 12 months of age, the percentages of subjects who achieved an hSBA seroresponse* for meningococcal serogroups A, C, Y, and W in Subgroup 1a were non-inferior to the corresponding percentages in Subgroup 2a.

- Null hypothesis (H0): p(men, G1a) - p(men, G2a) ≤ - 10%

- Alternative hypothesis (H1): p(men, G1a) - p(men, G2a) > - 10%

where p(men, G1a) and p(men, G2a) were the percentages of subjects who achieved hSBA vaccine seroresponse in Subgroup 1a and Subgroup 2a, respectively. Each of the serogroups A, C, Y, and W was tested separately. If the lower limit of the 2-sided 95% confidence interval (CI) of the difference between the 2 proportions was > - 10% for each serogroup, the inferiority assumption was rejected. For each of the 4 non-inferiority (NI) hypotheses using the vaccine seroresponse rates, the CI of the difference in proportions was computed using the Wilson Score method without continuity correction.

The overall NI of this objective was demonstrated if all 4 individual null hypotheses were rejected.

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

- For a subject with a pre-vaccination titer < 1:8, the post-vaccination titer should be ≥ 1:16
- For a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer should be ≥ 4-fold greater than the pre-vaccination titer

Primary hypothesis 2 (Ab titer ≥ 1:8 after the 3rd dose)

Thirty days after the administration of the 3rd dose of MenACYW conjugate vaccine or MENVEO at 6 months of age, the percentages of subjects who achieved hSBA ≥ 1:8 for meningococcal serogroups A, C, Y, and W in Group 1 were non-inferior to the corresponding percentages in Group 2.

- Null hypothesis (H0): p(men, G1) - p(men, G2) ≤ - 10%
- Alternative hypothesis (H1): p(men, G1) - p(men, G2) > - 10%

where p(men, G1) and p(men, G2) were the percentages of subjects who achieved hSBA ≥ 1:8 in Group 1 and Group 2, respectively. Each of the serogroups A, C, Y, and W was tested separately.

If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions was > - 10% for each serogroup, the inferiority assumption was rejected.

The overall NI of this objective was demonstrated if all 4 individual null hypotheses were rejected. For each of the 4 NI hypotheses using the percentage rates, the CI of the difference in proportions was computed using the Wilson Score method without continuity correction

Secondary objectives

I. First year evaluation at 30 days after the 6-month vaccinations (after the 3rd dose)

• Secondary Hypothesis 1 (Anti-hepatitis B % ≥ 10 mIU/mL)

Thirty days after the 6-month HB vaccine administration, the percentage of subjects who achieved ≥ 10 mIU/mL in anti-HB surface antibody concentrations in Group 1 was non-inferior to that in Group 2.

- Null hypothesis (H0): p(hep, G1) - p(hep, G2) ≤ - 10%.
- Alternative hypothesis (H1): p(hep, G1) - p(hep, G2) > - 10%.

where p(hep, G1) and p(hep, G2) were the percentages of subjects in Group 1 and Group 2, respectively, who achieved ≥ 10 mIU/mL in anti-HB surface antibody concentrations. If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions was > - 10%, the inferiority assumption was rejected.

• Secondary Hypothesis 2 (Anti-PRP % ≥ 0.15 μg/mL)

Thirty days after the 6-month Pentacel vaccination, the percentage of subjects who achieved ≥ 0.15 μg/mL in anti-PRP antibody concentrations in Group 1 was non-inferior to that in Group 2.

- Null hypothesis (H0): p(prp, G1) - p(prp, G2) ≤ - 5%
- Alternative hypothesis (H1): p(prp, G1) - p(prp, G2) > -5%

where p(prp, G1) and p(prp, G2) were the percentages of subjects in Group 1 and Group 2, respectively, who achieved ≥ 0.15 μg/mL in anti-PRP antibody concentrations. If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions was > -5%, the inferiority assumption was rejected.

• ***Secondary Hypothesis 3 (Anti-PRP % ≥ 1.0 μg/mL)***

Thirty days after the 6-month Pentacel vaccination, the percentage of subjects who achieved ≥ 1.0 μg/mL in anti-PRP antibody concentrations in Group 1 was non-inferior to that in Group 2.

- Null hypothesis (H0): p(prp, G1) - p(prp, G2) ≤ - 10%
- Alternative hypothesis (H1): p(prp, G1) - p(prp, G2) > - 10%

where p(prp, G1) and p(prp, G2) were the percentage of subjects in Group 1 and Group 2, respectively, who achieved ≥ 1.0 μg/mL in anti-PRP antibody concentrations. If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions was > - 10%, the inferiority assumption was rejected.

• ***Secondary Hypothesis 4 (Anti-polio % titer ≥ 1:8)***

Thirty days after the 6-month Pentacel vaccination, the percentages of subjects who achieved ≥ 1:8 in anti-polio antibody titers (type 1, type 2, and type 3) in Group 1 were non-inferior to those in Group 2.

- Null hypothesis (H0): p(pol, G1) - p(pol, G2) ≤ - 5%
- Alternative hypothesis (H1): p(pol, G1) - p(pol, G2) > - 5%

where p(pol, G1) and p(pol, G2) were the percentages of subjects in Group 1 and Group 2, respectively, who achieved ≥ 1:8 in anti-polio antibody titers (type 1, type 2, and type 3). Each of the antigens of type 1, type 2, and type 3 was tested separately. If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions was > - 5% for each type, the inferiority assumption was rejected.

• ***Secondary Hypothesis 5 (Anti- rotavirus % ≥ 3-fold rise)***

Thirty days after the 6-month rotavirus vaccine administration, the percentages of subjects who achieved ≥ 3-fold rise in serum IgA antibody concentrations against the rotavirus in Group 1 was non-inferior to those in Group 2.

- Null hypothesis (H0): p(rota, G1) - p(rota, G2) ≤ - 10%
- Alternative hypothesis (H1): p(rota, G1) - p(rota, G2) > -10%

where p(rota, G1) and p(rota, G2) were the percentages of subjects in Group 1 and Group 2, respectively, who achieved ≥ 3-fold rise in serum anti-rotavirus IgA antibody concentrations. If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions was > -10%, the inferiority assumption was rejected.

• ***Secondary Hypothesis 6 (Anti-rotavirus; GMC)***

Thirty days after the 6-month rotavirus vaccine administration, the GMCs of the serum IgA antibodies against the rotavirus in Group 1 were non-inferior to the GMCs in Group 2.

- Null hypothesis (H0): GMC(rota,G1) / GMC(rota, G2) ≤ 2/3
- Alternative hypothesis (H1): GMC(rota,G1) / GMC(rota, G2) > 2/3

where GMC(rota, G1) and GMC(rota,G2) were the GMCs of the serum IgA antibodies against the rotavirus in Group 1 and Group 2, respectively. If the lower limit of the 2-sided 95% CI of the ratio of the GMCs from the 2 groups was > 2/3, the inferiority assumption was rejected.

• Secondary Hypothesis 7 (Anti-pertussis; GMC)

Thirty days after the 6-month Pentacel vaccination, the GMCs of antibodies against the pertussis antigens (PT, FHA, PRN, and FIM) in Group 1 were non-inferior to the GMCs in Group 2.

- Null hypothesis (H0): GMC(pert,G1) / GMC(pert, G2) ≤ 2/3
- Alternative hypothesis (H1): GMC(pert,G1) / GMC(pert, G2) > 2/3

where GMC(pert, G1) and GMC(pert,G2) were the GMCs of antibodies against the pertussis antigens (PT, FHA, PRN, and FIM) in Group 1 and Group 2, respectively.

Each of the antigens of PT, FHA, PRN, and FIM were tested separately. If the lower limit of the 2-sided 95% CI of the ratio of the GMCs from the 2 groups was > 2/3 for each antigen, the inferiority assumption was rejected.

• Secondary Hypothesis 8 (Anti-pneumococcal; GMC)

Thirty days after the 6-month Prevnar 13® vaccination, the GMCs of antibodies against the pneumococcal antigens (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) in Group 1 were non-inferior to the GMCs in Group 2.

- Null hypothesis (H0): GMC(pne, G1) / GMC(pne, G2) ≤ 1/2
- Alternative hypothesis (H1): GMC(pne, G1) / GMC(pne, G2) >1/2

where GMC(pne, G1) and GMC(pne, G2) were the GMCs of antibodies against the pneumococcal antigens (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) in Group 1 and Group 2, respectively.

Each of the serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F were tested separately. If the lower limit of the 2-sided 95% CI of the ratio of the GMCs from the 2 groups was > 1/2 for each serotype, the inferiority assumption was rejected.

II. Second year evaluation at 30 days after the 12-month vaccinations

• Secondary Hypothesis 9 (Anti- measles % ≥ 255 mIU/mL)

Thirty days after the 12-month M-M-R® II vaccination, the percentages of subjects who achieved ≥ 255 mIU/mL in anti-measles antibody concentrations in Subgroup 1a were non-inferior to those in Subgroup 2a.

- Null hypothesis (H0): p(mea, G1a) - p(mea, G2a) ≤ - 10%
- Alternative hypothesis (H1): p(mea, G1a) - p(mea, G2a) > - 10%

where p(mea, G1a) and p(mea, G2a) were the percentages of subjects in Subgroup 1a and Subgroup 2a, respectively, who achieved ≥ 255 mIU/mL in anti-measles antibody concentrations.

If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions was > - 10%, the inferiority assumption was rejected.

• ***Secondary Hypothesis 10 (Anti-mumps% ≥ 10 mumps Ab units/mL)***

Thirty days after the 12-month M-M-R II vaccination, the percentages of subjects who achieved ≥10 mumps Ab units/mL in anti-mumps antibody concentrations in Subgroup 1a were non-inferior to those in Subgroup 2a.

- Null hypothesis (H0): p(mum, G1a) - p(mum, G2a) ≤ - 10%
- Alternative hypothesis (H1): p(mum, G1a) - p(mum, G2a) > -10%

where p(mum, G1a) and p(mum, G2a) were the percentages of subjects in Subgroup 1a and Subgroup 2a, respectively, who achieved ≥ 10 Mumps Ab units/mL in anti-mumps antibody concentrations. If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions was > - 10%, the inferiority assumption was rejected.

• ***Secondary Hypothesis 11 (Anti-rubella% ≥ 10 IU/mL)***

Thirty days after the 12-month M-M-R II vaccination, the percentages of subjects who achieved ≥ 10 IU/mL in anti-rubella antibody concentrations in Subgroup 1a were non-inferior to those in Subgroup 2a.

- Null hypothesis (H0): p(rub, G1a) - p(rub, G2a) ≤ - 10%
- Alternative hypothesis (H1): p(rub, G1a) - p(rub, G2a) > - 10%

where p(rub, G1a) and p(rub, G2a) were the percentage of subjects in Subgroup 1a and Subgroup 2a, respectively, who achieved ≥ 10 IU/mL in anti-rubella antibody concentrations. If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions was > - 10%, the inferiority assumption was rejected.

• ***Secondary Hypothesis 12 (Anti-varicella% ≥ 5 gpELISA Ab units/mL)***

Thirty days after the 12-month VARIVAX vaccination, the percentage of subjects who achieved ≥ 5 gpELISA units/mL in anti-varicella antibody concentrations in Subgroup 1a was non-inferior to those in Subgroup 2a.

- Null hypothesis (H0): p(var, G1a) - p(var, G2a) ≤ - 10%
- Alternative hypothesis (H1): p(var, G1a) - p(var, G2a) > - 10%

where p(var, G1a) and p(var, G2a) were the percentages of subjects in Subgroup 1a and Subgroup 2a, respectively, who achieved ≥ 5 gpELISA units/mL in anti-varicella antibody concentrations. If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions was >- 10%, the inferiority assumption was rejected.

• ***Secondary Hypothesis 13 (Anti-pneumococcal; GMC)***

Thirty days after the 12-month Prevnar13 vaccination, the GMCs of antibodies against the pneumococcal antigens (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) in Subgroup 1a were non-inferior to the GMCs in Subgroup 2a.

- Null hypothesis (H0): GMC(pne, G1a) / GMC(pne, G2a) ≤ 1/2
- Alternative hypothesis (H1): GMC(pne, G1a) / GMC(pne, G2a) > ½

where GMC(pne, G1a) and GMC(pne,G2a) were the GMCs of antibodies against the pneumococcal antigens (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) in Subgroup 1a and Subgroup 2a, respectively. Each of the serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F was tested separately. If the lower limit of the 2-sided 95% CI of the ratio of the GMCs from the 2 groups was > 1/2 for each serotype, the inferiority assumption was rejected.

III. Second year evaluation at 30 days after the 15-month vaccination

• Secondary Hypothesis 14 (Anti-PRP% ≥ 1.0 μg/mL)

Thirty days after the 15-month Pentacel vaccination, the percentage of subjects who achieved ≥ 1.0 μg/mL in anti-PRP antibody concentrations in Subgroup 1b was non-inferior to that in Subgroup 2b.

- Null hypothesis (H0): p(prp, G2b) - p(prp, G1b) ≤-10%
- Alternative hypothesis (H1): p(prp, G2b) - p(prp, G1b) > -10%

where p(prp, G1b) and p(prp, G2b) were the percentages of subjects in Subgroup 1b and Subgroup 2b, respectively, who achieved ≥ 1.0 μg/mL in anti-PRP antibody concentrations. If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions was > - 10%, the inferiority assumption was rejected.

• Secondary Hypothesis 15 (Anti-polio % titer ≥ 8)

Thirty days after the 15-month Pentacel vaccination, the percentages of subjects who achieved ≥ 1:8 in anti-polio antibody titers (type 1, type 2, and type 3) in Subgroup 1b were non-inferior to those in Subgroup 2b.

- Null hypothesis (H0): p(pol, G1b) - p(pol, G2b) ≤ - 5%
- Alternative hypothesis (H1): p(pol, G1b) - p(pol, G2b) > - 5%

where p(pol, G1b) and p(pol, G2b) were the percentages of subjects in Subgroup 1b and Subgroup 2b, respectively, who achieved ≥ 1:8 in anti-polio antibody titers (type 1, type 2, and type 3). Each of the antigens of type 1, type 2, and type 3 was tested separately. If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions was > - 5% for each serotype, the inferiority assumption was rejected.

• Secondary Hypothesis 16 (Anti-pertussis; vaccine response rate)

Thirty days after the 15-month Pentacel vaccination, the percentages of subjects with a pertussis vaccine response* for the pertussis antigens (PT, FHA, PRN, and FIM) in Subgroup 1b was non-inferior to the percentages in Subgroup 2b.

- Null hypothesis (H0): p(pert, G1b) - p(pert, G2b) ≤ - 10%
- Alternative hypothesis (H1): p(pert, G1b) - p(pert, G2b) > - 10%

where p(pert, G1b) and p(pert, G2b) were the percentages of subjects who achieved a pertussis vaccine response*in Subgroup 1b and Subgroup 2b, respectively. Each of the antigens of PT, FHA, PRN, and FIM was tested separately. If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions was > -10% for each antigen, the inferiority assumption was rejected.

*Pertussis vaccine response was defined as:

- Pre-booster (4th) vaccination concentration< LLOQ, then post- booster (4th) vaccination concentration had to be ≥ 4x the LLOQ

- Pre- booster (4th) vaccination concentration ≥ LLOQ but < 4x the LLOQ, then post- booster (4th) vaccination concentration had to achieve a 4-fold rise (post-4th vaccination/ Pre-4th vaccination ≥ 4)
- Pre- booster (4th) vaccination concentration ≥ 4x the LLOQ, then post- booster (4th) vaccination concentration had to achieve a 2-fold response (post-4th vaccination/ Pre-4th vaccination ≥ 2)

iii. Secondary immunogenicity objectives 2 to 6

All immunogenicity analysis were descriptive. In general, categorical variables were summarized and presented by frequency counts, proportion percentages and CIs. The 95% CIs of point estimates were calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for proportions. For geometric mean titers (GMTs) and GMCs, 95% CIs of point estimates were calculated using normal approximation assuming they are log-normally distributed.

The summary of NI hypothesis for the secondary objectives is presented in Table 4.

Table 4: Summary of non-inferiority hypotheses for the secondary objectives

Evaluation Time	Comparison Groups (G)	Antigen	Endpoint	Non-inferiority margin	Hypothesis #
1st year, 30 days after the 6-month vaccinations	G1 vs G2	Hepatitis B	% ≥ 10 mIU/mL	10%	1
		PRP	% ≥ 0.15 µg/mL	5%	2
		PRP	% ≥ 1.0 µg/mL	10%	3
		Polio†	% ≥ 1:8	5%	4
		Rotavirus	% ≥ 3-fold rise	10%	5
		Rotavirus	GMC (G1/G2 ratio)	1.5	6
		Pertussis*	GMC (G1/G2 ratio)	1.5	7
		Pneumococcal‡	GMC (G1/G2 ratio)	2	8
2nd year, 30 days after the 12-month vaccinations	G1a vs G2a	Measles	% ≥ 255 mIU/mL	10%	9
		Mumps	% ≥ 10 mumps Ab units/mL	10%	10
		Rubella	% ≥ 10 IU/mL	10%	11
		Varicella	% ≥ 5 gpELISA units/ml	10%	12
		Pneumococcal‡	GMC (G1a/G2a ratio)	2	13
2nd year, 30 days after the 15-month vaccinations	G1b vs G2b	PRP	% ≥ 1.0 µg/mL	10%	14
		Polio†	% ≥ 1:8	5%	15
		Pertussis*	Response rate	10%	16

* Pertussis: PT, FHA, PRN, and FIM
† Polio: type 1, type 2, type 3
‡ Pneumococcal: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F

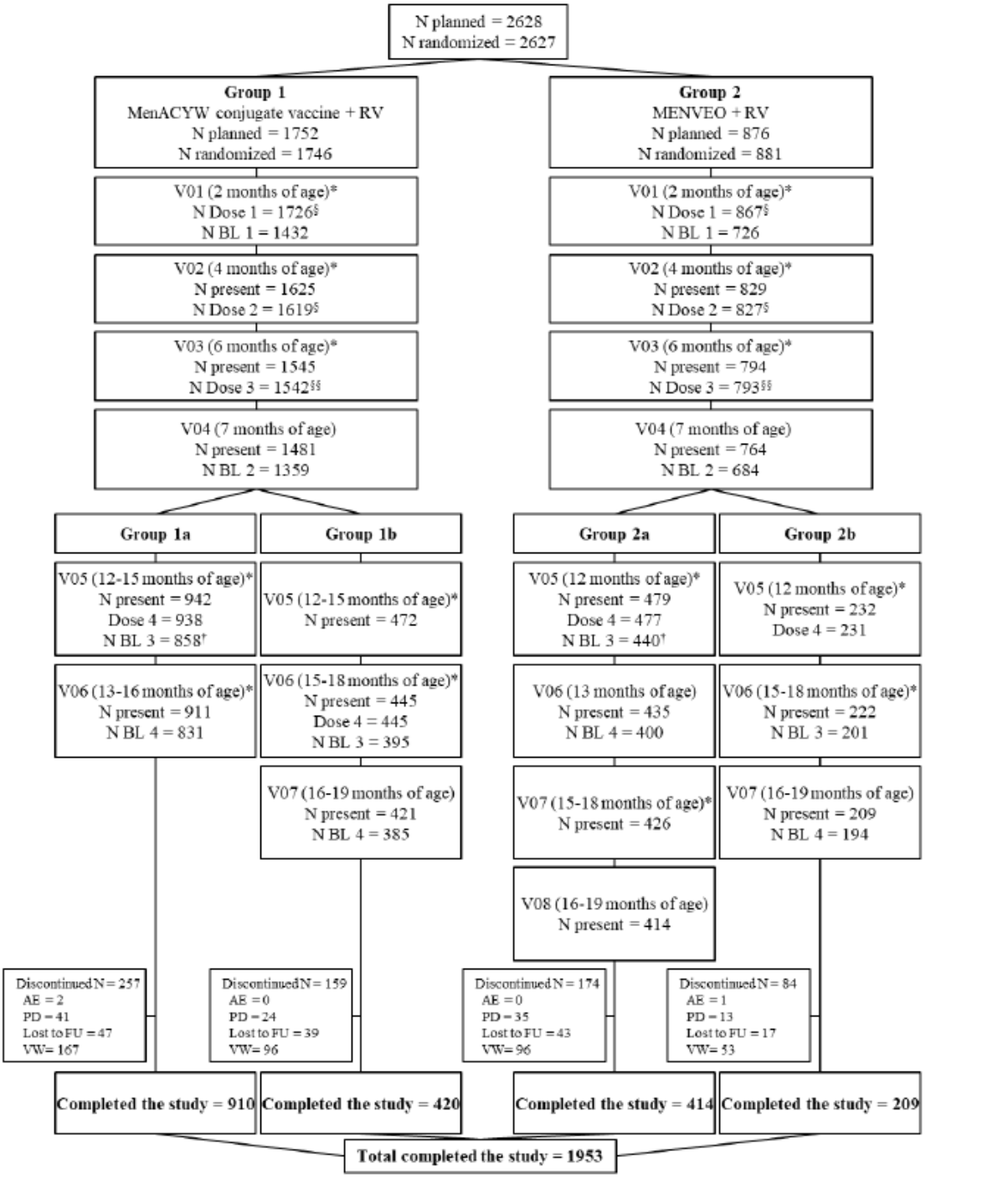
iv. Observational objectives

Safety / Reactogenicity

Safety results were described for subjects in all study groups. The main parameters for the safety endpoints were described by 95% CIs (based on the Clopper-Pearson method).

Results

Participant flow



Abbreviations: AE, adverse event; BL, blood sample; FU, follow up; PD, protocol deviation; RV, routine vaccines; V, visit; VW, voluntary withdrawal by parent(s)/LAR(s)
*Subjects received pediatric routine vaccines at the indicated visits according to the ACIP recommendations.
§In Group 2, 1 subject at V01 and 1 subject at V02 received MenACYW conjugate vaccine instead of MENVEO.
§§ In Group 1, 1 subject received MENVEO instead of MenACYW conjugate vaccine at V03.
†One subject in Group 1b and 3 subjects in Group 2b had an unplanned blood sampling at V05.

Figure 1: Subject disposition flowchart

Recruitment

Approximately 2628 healthy infants aged ≥ 42 to ≤ 89 days were planned. A total of 2627 subjects were enrolled and randomized between 25 April 2018 and 12 November 2021 in the study.

Baseline data

Table 5: Baseline demographics by randomized group - All Randomized Subjects

	Group 1 (N=1746)	Group 2 (N=881)	Group 1a (N=1167)	Group 1b (N=579)	Group 2a (N=588)	Group 2b (N=293)	All (N=2627)
Sex: n (%)							
Male	918 (52.6)	466 (52.9)	618 (53.0)	300 (51.8)	324 (55.1)	142 (48.5)	1384 (52.7)
Female	828 (47.4)	415 (47.1)	549 (47.0)	279 (48.2)	264 (44.9)	151 (51.5)	1243 (47.3)
Sex ratio: Male/Female	1.11	1.12	1.13	1.08	1.23	0.94	1.11
Age: (Days)							
M	1746	881	1167	579	588	293	2627
Mean (SD)	65.3 (8.02)	65.3 (7.81)	65.3 (8.12)	65.3 (7.80)	65.4 (7.75)	65.0 (7.93)	65.3 (7.95)
Min ; Max	42.0 ; 89.0	42.0 ; 89.0	42.0 ; 89.0	42.0 ; 89.0	42.0 ; 89.0	42.0 ; 89.0	42.0 ; 89.0
Median	64.0	64.0	64.0	64.0	64.0	64.0	64.0
Q1 ; Q3	61.0 ; 69.0	61.0 ; 69.0	61.0 ; 69.0	61.0 ; 69.0	61.0 ; 69.0	61.0 ; 69.0	61.0 ; 69.0
Racial origin: n (%)							
American Indian or Alaska Native	11 (0.6)	3 (0.3)	6 (0.5)	5 (0.9)	3 (0.5)	0	14 (0.5)
Asian	15 (0.9)	10 (1.1)	8 (0.7)	7 (1.2)	6 (1.0)	4 (1.4)	25 (1.0)
Black or African American	204 (11.7)	99 (11.2)	142 (12.2)	62 (10.7)	63 (10.7)	36 (12.3)	303 (11.5)
Native Hawaiian or Other Pacific Islander	7 (0.4)	6 (0.7)	5 (0.4)	2 (0.3)	4 (0.7)	2 (0.7)	13 (0.5)
White	1428 (81.8)	722 (82.0)	950 (81.4)	478 (82.6)	491 (83.5)	231 (78.8)	2150 (81.8)
Mixed Origin	44 (2.5)	30 (3.4)	31 (2.7)	13 (2.2)	16 (2.7)	14 (4.8)	74 (2.8)
Unknown	19 (1.1)	6 (0.7)	14 (1.2)	5 (0.9)	3 (0.5)	3 (1.0)	25 (1.0)
Not Reported	18 (1.0)	5 (0.6)	11 (0.9)	7 (1.2)	2 (0.3)	3 (1.0)	23 (0.9)
Ethnicity: n (%)							
Hispanic or Latino	838 (48.0)	410 (46.5)	549 (47.0)	289 (49.9)	278 (47.3)	132 (45.1)	1248 (47.5)
Not Hispanic or Latino	897 (51.4)	465 (52.8)	611 (52.4)	286 (49.4)	305 (51.9)	160 (54.6)	1362 (51.8)
Unknown	3 (0.2)	4 (0.5)	2 (0.2)	1 (0.2)	3 (0.5)	1 (0.3)	7 (0.3)
Not Reported	8 (0.5)	2 (0.2)	5 (0.4)	3 (0.5)	2 (0.3)	0	10 (0.4)

n: number of subjects fulfilling the item listed in the first column

M: number of subjects with available data for the relevant endpoint

N: number of subjects randomized in each study group

Percentages are based on N. Q1; Q3: first quartile; third quartile. SD: standard deviation

Group 1 (Group 1a and 1b): MenACYW conjugate vaccine and routine pediatric vaccines

Group 2 (Group 2a and 2b): MENVEO® and routine pediatric vaccines

Number analysed

Please also refer to section "Participant flow".

Table 6: Immunogenicity analysis sets by randomized group for infant stage - All Randomized Subjects

	Group 1 (N=1746) n (%)	Group 2 (N=881) n (%)	All (N=2627) n (%)
Full Analysis Set 1	1339 (76.7)	663 (75.3)	2002 (76.2)
Subjects with at least one criterion for exclusion from FAS1	407 (23.3)	218 (24.7)	625 (23.8)
Not injected study vaccine at Visit 1 to Visit 3	19 (1.1)	12 (1.4)	31 (1.2)
Did not have a valid post-vaccination serology result at Visit 4	407 (23.3)	218 (24.7)	625 (23.8)
Per Protocol Analysis Set 1	928 (53.2)	460 (52.2)	1388 (52.8)
Subjects with at least one deviation	818 (46.8)	421 (47.8)	1239 (47.2)
Did not meet all protocol-specified inclusion/exclusion criteria	5 (0.3)	6 (0.7)	11 (0.4)
Did not complete the vaccinations schedule for infant stage from Visit 1 to Visit 3	217 (12.4)	94 (10.7)	311 (11.8)
Received vaccine other than randomized from Visit 1 to Visit 3	1 (<0.1)	2 (0.2)	3 (0.1)
Vaccine not prepared/administered as per-protocol from Visit 1 to Visit 3	47 (2.7)	21 (2.4)	68 (2.6)
Did not receive vaccine in time window	367 (21.0)	189 (21.5)	556 (21.2)
Did not provide a post-dose serology sample	387 (22.2)	197 (22.4)	584 (22.2)
Post-dose serology sample not in time window	141 (8.1)	70 (7.9)	211 (8.0)
Received protocol-prohibited therapy/medication/vaccine	42 (2.4)	11 (1.2)	53 (2.0)
Did not provide a valid blood test result	407 (23.3)	218 (24.7)	625 (23.8)
Other protocol deviations	0	0	0

n: number of subjects fulfilling the item listed
N: total number of subjects randomized in each study group
Note: A subject may be associated with more than 1 deviation.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines
Group 2: MENVEO® and routine pediatric vaccines

Table 7: Immunogenicity analysis sets by randomized group for immunogenicity persistence evaluations - All Randomized Subjects

	Group 1a (N=1167) n (%)	Group 1b (N=579) n (%)	Group 2a (N=588) n (%)	Group 2b (N=293) n (%)	All (N=2627) n (%)
Full Analysis Set 2	844 (72.3)	388 (67.0)	434 (73.8)	200 (68.3)	1866 (71.0)
Subjects with at least one criterion for exclusion from FAS2	323 (27.7)	191 (33.0)	154 (26.2)	93 (31.7)	761 (29.0)
Not injected study vaccine at Visit 1 to Visit 3	11 (0.9)	8 (1.4)	8 (1.4)	4 (1.4)	31 (1.2)
Did not have a valid post-vaccination serology result at Visit 5 or Visit 6	323 (27.7)	191 (33.0)	154 (26.2)	93 (31.7)	761 (29.0)
Per Protocol Analysis Set 2	647 (55.4)	295 (50.9)	329 (56.0)	157 (53.6)	1428 (54.4)
Subjects with at least one deviation	520 (44.6)	284 (49.1)	259 (44.0)	136 (46.4)	1199 (45.6)
Did not meet all protocol-specified inclusion/exclusion criteria	4 (0.3)	1 (0.2)	3 (0.5)	3 (1.0)	11 (0.4)
Did not complete the vaccinations schedule for infant stage	143 (12.3)	74 (12.8)	63 (10.7)	31 (10.6)	311 (11.8)
Received vaccine other than randomized	1 (<0.1)	0	1 (0.2)	1 (0.3)	3 (0.1)
Vaccine not prepared/administered as per-protocol	29 (2.5)	18 (3.1)	15 (2.6)	6 (2.0)	68 (2.6)
Did not receive vaccine in time window	247 (21.2)	120 (20.7)	136 (23.1)	53 (18.1)	556 (21.2)
Did not provide a pre-dose serology sample	309 (26.5)	184 (31.8)	148 (25.2)	92 (31.4)	733 (27.9)
Received protocol-prohibited therapy/medication/vaccine	2 (0.2)	4 (0.7)	2 (0.3)	1 (0.3)	9 (0.3)
Did not provide a valid blood test result	323 (27.7)	191 (33.0)	154 (26.2)	93 (31.7)	761 (29.0)
Other protocol deviations	0	0	0	1 (0.3)	1 (<0.1)

n: number of subjects fulfilling the item listed; N: total number of subjects randomized in each study group
Note: A subject may be associated with more than 1 deviation.
Group 1a: MenACYW conjugate vaccine and routine vaccines at 2, 4, 6, and 12 to 15 months of age
Group 1b: MenACYW conjugate vaccine at 2, 4, 6, and 15 to18 months of age and routine vaccines at 2, 4, 6, 12 to 15 months of age
Group 2a: MENVEO® at 2, 4, 6, and 12 months of age and routine vaccines at 2, 4, 6, 12, and 15 to 18 months of age. Blood samples collected for 12-month vaccination
Group 2b: MENVEO® at 2, 4, 6, and 12 months of age and routine vaccines at 2, 4, 6, 12, and 15 to 18 months of age. Blood samples collected for 15-month vaccination

Table 8: Immunogenicity analysis sets by randomized group for 2nd year of life - All Randomized Subjects

	Group 1a (N=1167) n (%)	Group 1b (N=579) n (%)	Group 2a (N=588) n (%)	Group 2b (N=293) n (%)	All (N=2627) n (%)
Full Analysis Set 3	816 (69.9)	378 (65.3)	398 (67.7)	193 (65.9)	1785 (67.9)
Subjects with at least one criterion for exclusion from FAS3	351 (30.1)	201 (34.7)	190 (32.3)	100 (34.1)	842 (32.1)
Not injected study vaccine at Visit 5 to Visit 7	228 (19.5)	107 (18.5)	111 (18.9)	62 (21.2)	508 (19.3)
Did not have a valid post-vaccination serology result at Visit 6 or Visit 7	351 (30.1)	201 (34.7)	190 (32.3)	100 (34.1)	842 (32.1)
Per Protocol Analysis Set 3	675 (57.8)	308 (53.2)	308 (52.4)	126 (43.0)	1417 (53.9)
Subjects with at least one deviation	492 (42.2)	271 (46.8)	280 (47.6)	167 (57.0)	1210 (46.1)
Did not meet all protocol-specified inclusion/exclusion criteria	4 (0.3)	1 (0.2)	3 (0.5)	3 (1.0)	11 (0.4)
Did not complete the vaccinations schedule for infant and the second year of the study	243 (20.8)	142 (24.5)	118 (20.1)	74 (25.3)	577 (22.0)
Received vaccine other than randomized	1 (<0.1)	0	1 (0.2)	1 (0.3)	3 (0.1)
Vaccine not prepared/administered as per-protocol	40 (3.4)	20 (3.5)	20 (3.4)	9 (3.1)	89 (3.4)
Did not receive vaccine in time window	13 (1.1)	24 (4.1)	54 (9.2)	43 (14.7)	134 (5.1)
Did not provide a post-dose serology sample	336 (28.8)	194 (33.5)	188 (32.0)	99 (33.8)	817 (31.1)
Post-dose serology sample not in time window	99 (8.5)	47 (8.1)	37 (6.3)	28 (9.6)	211 (8.0)
Received protocol-prohibited therapy/medication/vaccine	9 (0.8)	5 (0.9)	9 (1.5)	3 (1.0)	26 (1.0)
Did not provide a valid blood test result	351 (30.1)	201 (34.7)	190 (32.3)	100 (34.1)	842 (32.1)
Other protocol deviations	0	0	0	1 (0.3)	1 (<0.1)

n: number of subjects fulfilling the item listed; N: total number of subjects randomized in each study group
Note: A subject may be associated with more than 1 deviation.
Group 1a: MenACYW conjugate vaccine and routine vaccines at 2, 4, 6, and 12 to 15 months of age
Group 1b: MenACYW conjugate vaccine at 2, 4, 6, and 15 to18 months of age and routine vaccines at 2, 4, 6, 12 to 15 months of age
Group 2a: MENVEO® at 2, 4, 6, and 12 months of age and routine vaccines at 2, 4, 6, 12, and 15 to 18 months of age. Blood samples collected for 12-month vaccination
Group 2b: MENVEO® at 2, 4, 6, and 12 months of age and routine vaccines at 2, 4, 6, 12, and 15 to 18 months of age. Blood samples collected for 15-month vaccination

Table 9: Safety analysis set by vaccinations group - All randomized subjects

	Group 1 (N=1727) n (%)	Group 2 (N=867) n (%)	Group 1a (N=938) n (%)	Group 1b (N=472) n (%)	Group 2a (N=480) n (%)	Group 2b (N=228) n (%)	Randomized but not vaccinated (N=31) n (%)	All (N=2627) n (%)
Overall safety analysis set for any dose	1727 (100)	867 (100)	-	-	-	-	-	2594 (98.7)
Safety analysis set for vaccinations at 2 months of age	1727 (100)	867 (100)	-	-	-	-	-	2594 (98.7)
Safety analysis set for vaccinations at 4 months of age	1620 (93.8)	827 (95.4)	-	-	-	-	-	2447 (93.1)
Safety analysis set for vaccinations at 6 months of age	1542 (89.3)	794 (91.6)	-	-	-	-	-	2336 (88.9)
Safety analysis set for vaccinations at 12 months of age	-	-	938 (100)	472 (100)	480 (100)	228 (100)	-	2118 (80.6)
Safety analysis set for vaccinations at 15 months of age	-	-	-	444 (94.1)	425 (88.5)	219 (96.1)	-	1088 (41.4)
Safety analysis set for all 4-dose vaccination*	1375 (79.6)	705 (81.3)	-	-	-	-	-	2080 (79.2)

n: number of subjects experiencing the endpoint; N and n are based on actual vaccination group. Percentages are based on N.
Subjects received vaccine is defined as subjects who received at least 1 dose of study vaccines, including MenACYW conjugate vaccine, Menveo ® or the routine vaccines
Safety analysis set is defined as subjects who received at least 1 dose of study vaccines and for whom any safety data are available
*All 4-dose vaccinations received in a series (without vaccinations window restrictions) should be either all MenACYW or all Menveo ®
Group 1 (Group 1a and 1b): MenACYW conjugate vaccine and routine pediatric vaccines
Group 2 (Group 2a and 2b): MENVEO® and routine pediatric vaccines
At visit 1, 2 subjects did not receive any IMP (MenACYW or Menveo).

Efficacy/Immunogenicity results

Co-primary Immunogenicity Objective #1

The co-primary objective #1 was to demonstrate the NI of the hSBA vaccine seroresponse to meningococcal serogroups A, C, Y, and W following the administration of a 4-dose series of MenACYW conjugate vaccine compared to a 4-dose series of MENVEO when given concomitantly with routine pediatric vaccines to infants and toddlers 6 weeks of age to 15 months of age.

The NI of hSBA vaccine seroresponse rate at D30 after the 4th dose of MenACYW conjugate vaccine administered at 12 to 15 months of age (Group 1a) or MENVEO administered at 12 months of age (Group 2a) in the PPAS3 is presented in Table 10.

The co-primary objective #1 was met. At D30 after the 4th dose, the NI of MenACYW conjugate vaccine (Group 1a) compared to MENVEO (Group 2a) was demonstrated in the PPAS3 as the lower limit of the 95% confidence interval (CI) of the difference in the proportion of subjects with an hSBA seroresponse rate for meningococcal serogroups A, C, W, and Y was greater than -10%.

At D30 after the 4th dose in the PPAS3, the hSBA vaccine seroresponse rates were:

- for serogroup A: 79.4% in Group 1a and 77.6% in Group 2a

- for serogroup C: 97.0% in Group 1a and 88.2% in Group 2a
- for serogroup Y: 96.4% in Group 1a and 92.3% in Group 2a
- for serogroup W: 97.6% in Group 1a and 96.4% in Group 2a

The NI was also demonstrated in the FAS3.

Table 10: Non-inferiority of hSBA vaccine seroresponse rate at D30 after the 4th dose - Per-Protocol Analysis Set 3

	Group 1a (N=675)			Group 2a (N=308)			Group 1a - Group 2a		
Serogroup	n/M	Seroresponse rate (%)	95% CI	n/M	Seroresponse rate (%)	95% CI	Difference (%)	95% CI	Non-inferiority
A	398/501	79.4	(75.6 ; 82.9)	173/223	77.6	(71.5 ; 82.9)	1.86	(-4.38 ; 8.64)	Yes
C	514/530	97.0	(95.1 ; 98.3)	210/238	88.2	(83.4 ; 92.0)	8.75	(4.80 ; 13.60)	Yes
Y	504/523	96.4	(94.4 ; 97.8)	215/233	92.3	(88.1 ; 95.4)	4.09	(0.68 ; 8.44)	Yes
W	527/540	97.6	(95.9 ; 98.7)	241/250	96.4	(93.3 ; 98.3)	1.19	(-1.18 ; 4.45)	Yes

n: Number of subjects who achieve the hSBA vaccine seroresponse.
N: number of subjects in per-protocol analysis set 3, for 2nd year of life vaccinations; M: number of subjects with available data for the relevant endpoint
hSBA vaccine seroresponse: for a subject with a pre-1st dose (D0 before 2-month) vaccinations titer < 1:8, the post-4th dose (D30 after 12-month) vaccinations titer must be >= 1:16;
For a subject with a pre-1st dose vaccinations titer >= 1:8, the post-4th vaccinations titer must be at least 4-fold greater than the pre-1st dose vaccinations titer.
95% CI of the single proportion calculated from the exact binomial method. ; 95% CI of the difference calculated from the Wilson Score method without continuity correction.
The overall non-inferiority will be demonstrated if the lower limit of the 2-sided 95% CI is > -10% for all four serogroups.
Group 1a: MenACYW conjugate vaccine and routine vaccines at 2, 4, 6, and 12 to 15 months of age
Group 2a: MENVEO® at 2, 4, 6, and 12 months of age and routine vaccines at 2, 4, 6, 12, and 15 to 18 months of age

Co-primary Immunogenicity Objective #2

The co-primary objective #2 was to demonstrate the NI of the hSBA Ab response to meningococcal serogroups A, C, Y, and W following the administration of 3 doses in infancy of MenACYW conjugate vaccine (Group 1) compared to 3 doses in infancy of MENVEO (Group 2) when given concomitantly with routine pediatric vaccines to infants at 2, 4, and 6 months of age.

The NI of the percentage of subjects with hSBA titers ≥ 1:8 at D30 after the 3rd dose of MenACYW conjugate vaccine (Group 1) or MENVEO (Group 2) administered at 6 months of age in the PPAS1 is presented in Table 11.

The co-primary objective #2 was met. At D30 after the 3rd dose, the NI of MenACYW conjugate vaccine (Group 1) compared to MENVEO (Group 2) was demonstrated in the PPAS1 as the lower limit of the 95% CI of the difference in the proportion of subjects who achieved hSBA titers ≥ 1:8 for serogroups A, C, W, and Y was greater than -10%.

At D30 after the 3rd dose, the percentages of subjects with hSBA antibody titers ≥ 1:8 were:

- for serogroup A: 77.9% in Group 1 and 67.7% in Group 2
- for serogroup C: 99.0% in Group 1 and 91.2% in Group 2
- for serogroup Y: 98.3% in Group 1 and 91.7% in Group 2
- for serogroup W: 98.6% in Group 1 and 92.9% in Group 2

The NI was also demonstrated in the FAS1.

Table 11: Non-inferiority of the percentage of subjects with hSBA antibody titers >=1:8 at D30 after the 3rd dose - Per-Protocol Analysis Set 1

	Group 1 (N=928)			Group 2 (N=460)			Group 1 - Group 2		
Serogroup	n/M	%	95% CI	n/M	%	95% CI	Difference (%)	95% CI	Non-inferiority
A	664/852	77.9	(75.0 ; 80.7)	277/409	67.7	(63.0 ; 72.2)	10.21	(4.98 ; 15.59)	Yes
C	827/835	99.0	(98.1 ; 99.6)	384/421	91.2	(88.1 ; 93.7)	7.83	(5.31 ; 10.96)	Yes
Y	846/861	98.3	(97.1 ; 99.0)	388/423	91.7	(88.7 ; 94.2)	6.53	(4.01 ; 9.62)	Yes
W	871/883	98.6	(97.6 ; 99.3)	407/438	92.9	(90.1 ; 95.1)	5.72	(3.44 ; 8.57)	Yes

n: Number of subjects with hSBA antibody titers that met the criterion.
M: Number of subjects with available data for the endpoint.
N: number of subjects in per-protocol analysis set 1, for infant vaccinations
95% CI of the single proportion calculated from the exact binomial method.
95% CI of the difference calculated from the Wilson Score method without continuity correction
The overall non-inferiority will be demonstrated if the lower limit of the 2-sided 95% CI is > -10% for all four serogroups
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines
Group 2: MENVEO® and routine pediatric vaccines

Secondary Objective #1: Non-Inferiority of Routine Pediatric Vaccines Administered Concomitantly With MenACYW Conjugate Vaccine or MENVEO

The secondary objective #1 was met: the NI of immune responses of the routine pediatric vaccines administered concomitantly with MenACYW conjugate vaccine as compared with MENVEO in infants and toddlers 6 weeks old to 18 months old was demonstrated (Table 12).

The NI was also demonstrated for all antigens in the FAS1 and in the FAS3.

Table 12: Summary of non-inferiority results for the secondary objective #1

Antigen	Endpoint	NI margin	NI demonstrated
At D30 after the 6-month vaccinations (Group 1 vs Group 2 in the PPAS1)			
Hepatitis B	% ≥ 10 mIU/mL	10%	Yes: Difference G1 - G2 0.57% (95% CI: -0.95; 2.75)
PRP	% ≥ 0.15 µg/mL	5%	Yes: Difference G1 - G2 2.55% (95% CI: 0.89; 4.84)
PRP	% ≥ 1.0 µg/mL	10%	Yes: Difference G1 - G2 5.56% (95% CI: 1.90; 9.60)
Polio	% ≥ 1:8	5%	Yes: Difference G1 - G2 Type 1: 0% (95% CI: -0.46; 0.92) Type 2: 0% (95% CI: -0.46; 0.94) Type 3: 0% (95% CI: -0.45; 0.92)
Rotavirus	% ≥ 3-fold rise	10%	Yes: Difference G1 - G2 -1.88% (95% CI: -5.26; 2.00)
Rotavirus	GMC (G1/G2 ratio)	1.5	Yes: GMC (G1/G2) ratio 0.881 (95% CI: 0.728; 1.07)
Pertussis	GMC (G1/G2 ratio)	1.5	Yes: GMC (G1/G2) ratios PT: 0.964 (95% CI: 0.880; 1.06) FHA: 0.970 (95% CI: 0.887; 1.06) PRN: 0.938 (95% CI: 0.830; 1.06) FIM: 0.996 (95% CI: 0.892; 1.11)
Pneumococcal	GMC (G1/G2 ratio)	2	Yes: GMC (G1/G2) ratios Serotype 1: 1.17 (95% CI: 1.05; 1.30) Serotype 3: 1.12 (95% CI: 1.02; 1.22) Serotype 4: 1.10 (95% CI: 1.01; 1.19) Serotype 5: 1.23 (95% CI:1.11; 1.36) Serotype 6A: 1.20 (95% CI: 1.09; 1.32) Serotype 6B: 1.26 (95% CI: 1.09; 1.44) Serotype 7F: 1.02 (95% CI: 0.946; 1.11) Serotype 9V: 1.17 (95% CI : 1.06; 1.29) Serotype 14: 0.970 (95% CI: 0.870; 1.08) Serotype 18C: 1.07 (95% CI: 0.983; 1.16) Serotype 19A: 1.10 (95% CI: 1.01; 1.20) Serotype 19F: 1.13 (95% CI: 1.03; 1.23) Serotype 23F: 1.22 (95% CI: 1.09; 1.37)
At D30 after the 12-month vaccinations (Group 1a vs Group 2a in the PPAS3)			
Measles	% ≥ 255 mIU/mL	10%	Yes: Difference G1a - G2a 0.24% (95% CI: -1.73; 2.90)
Mumps	% ≥ 10 mumps Ab units/mL	10%	Yes: Difference G1a - G2a -2.22% (95% CI: -4.44; 0.53)
Rubella	% ≥ 10 IU/mL	10%	Yes: Difference G1a - G2a -0.12% (95% CI: -1.89; 2.32)

Varicella	% ≥ 5 gpELISA units/ml	10%	Yes: Difference G1a - G2a 1.69% (95% CI: -0.96; 5.05)
Pneumococcal	GMC (G1a/G2a ratio)	2	Yes: GMC (G1a/G2a) ratios Serotype 1: 1.11 (95% CI: 0.980; 1.25) Serotype 3: 1.03 (95% CI: 0.927; 1.14) Serotype 4: 1.04 (95% CI: 0.933; 1.16) Serotype 5: 1.10 (95% CI: 0.980; 1.23) Serotype 6A: 1.01 (95% CI : 0.912; 1.13) Serotype 6B: 1.16 (95% CI: 1.03; 1.31) Serotype 7F: 0.894 (95% CI: 0.806; 0.992) Serotype 9V: 0.976 (95% CI: 0.871; 1.09) Serotype 14: 0.847 (95% CI: 0.752; 0.954) Serotype 18C: 0.890 (95% CI: 0.799; 0.992) Serotype 19A: 1.06 (95% CI: 0.945; 1.18) Serotype 19F: 1.08 (95% CI: 0.967; 1.21) Serotype 23F: 1.14 (95% CI: 0.999; 1.29)
At D30 after the 15-month vaccinations Group 1b vs Group 2b in the PPAS3			
PRP	% ≥ 1.0 µg/mL	10%	Yes: Difference G1b - G2b -0.08% (95% CI: -2.57; 4.08)
Polio	% ≥ 1:8	5%	Yes: Difference G1b - G2b Type 1: 0% (95% CI: -1.33; 3.05) Type 2: 0% (95% CI: -1.30; 3.05) Type 3: 0% (95% CI: -1.31; 3.05)
Pertussis	Response rate	10%	Yes: Difference G1b - G2b PT: 0.19 (95% CI: -2.35; 4.46) FHA: 0.01 (95% CI: -3.48; 5.14) PRN: -1.18 (95% CI: -4.55; 3.67) FIM: 0.65 (95% CI: -2.24; 5.32)

Secondary Objective #2: Antibody Responses After the 4th Dose of MenACYW Conjugate Vaccine or MENVEO at 12 Months of Age

For all reported results comparable results were observed in the respective full analysis sets or otherwise reported here.

hSBA GMTs After the 4th Dose of MenACYW Conjugate Vaccine or MENVEO

A summary of hSBA meningococcal serogroups A, C, Y, and W geometric mean titers (GMTs) at D0 before and at D30 after the 12-month vaccinations in the PPAS3 is presented in Table 13.

In the PPAS3 (subjects vaccinated at Visit 5 with valid pre- and post-4th dose serology results at Visit 6 and no exclusionary protocol deviations) at D0 before the 4th dose, the hSBA GMTs for meningococcal serogroups A, C, Y, and W were higher in Group 1a than in Group 2a. The hSBA GMTs were:

- for serogroup A: 10.6 in Group 1a and 6.64 in Group 2a
- for serogroup C: 61.3 in Group 1a and 4.45 in Group 2a

- for serogroup Y: 43.5 in Group 1a and 9.97 in Group 2a
- for serogroup W: 57.9 in Group 1a and 9.02 in Group 2a

In the PPAS3, at D30 after the 4th dose, the hSBA GMTs were comparable between both groups for serogroup A and higher in Group 1a than in Group 2a for serogroups C, Y, and W. The hSBA GMTs were:

- for serogroup A: 67.1 in Group 1a and 56.9 in Group 2a
- for serogroup C: 678 in Group 1a and 90.9 in Group 2a
- for serogroup Y: 296 in Group 1a and 186 in Group 2a
- for serogroup W: 387 in Group 1a and 175 in Group 2a

Table 13: Summary of geomtric means of hSBA titers at D0 before D30 after 12-month vaccinations for Groups 1a and 2a – Per-Protocol Analysis Set 3

		Group 1a (N=675)			Group 2a (N=308)		
Serogroup	Time Point	M	GMT	95% CI	M	GMT	95% CI
A	D0 before 4th dose	607	10.6	(9.54 ; 11.8)	282	6.64	(5.74 ; 7.68)
	D30 after 4th dose	642	67.1	(58.1 ; 77.5)	296	56.9	(46.7 ; 69.5)
C	D0 before 4th dose	612	61.3	(54.4 ; 69.0)	284	4.45	(3.91 ; 5.08)
	D30 after 4th dose	655	678	(606 ; 758)	300	90.9	(75.7 ; 109)
Y	D0 before 4th dose	611	43.5	(39.7 ; 47.6)	287	9.97	(8.72 ; 11.4)
	D30 after 4th dose	651	296	(268 ; 327)	295	186	(158 ; 219)
W	D0 before 4th dose	619	57.9	(52.7 ; 63.7)	288	9.02	(7.88 ; 10.3)
	D30 after 4th dose	651	387	(352 ; 426)	305	175	(149 ; 206)

N : number of subjects in per-protocol analysis set 3, for 2nd year of life vaccinations
M: number of subjects with valid serology results for the particular serogroup and time point
95% CI calculated using calculation for normal distribution on log10(titer) following by antilog transformation
Group 1a: MenACYW conjugate vaccine and routine vaccines at 2, 4, 6, and 12 to 15 months of age
Group 2a: MENVEO® at 2, 4, 6, and 12 months of age and routine vaccines at 2, 4, 6, 12, and 15 to 18 months of age

hSBA Titers ≥ 4-fold Rise From Pre- to Post-4th Dose of MenACYW Conjugate Vaccine or MENVEO

In the PPAS3, the percentages of subjects with ≥ 4-fold rise of hSBA titer from pre-4th dose to post-4th dose at 12 to 15 months of age were comparable between both groups for serogroups A and C, and higher in Group 2a than in Group 1a for serogroups Y and W. The percentages of subjects with a ≥ 4-fold rise of hSBA titer were:

- for serogroup A: 66.3% in Group 1a and 73.2% in Group 2a
- for serogroup C: 90.3% in Group 1a and 87.1% in Group 2a
- for serogroup Y: 80.2% in Group 1a and 93.1% in Group 2a
- for serogroup W: 80.4% in Group 1a and 91.9% in Group 2a

Secondary Objective #3: Persistence of Bactericidal Antibodies After the 3rd Dose of MenACYW *Conjugate Vaccine or MENVEO*

For all reported results comparable results were observed in the respective full analysis sets or otherwise reported here.

hSBA GMTs After the 3rd Dose and Before the 4th Dose of MenACYW Conjugate Vaccine or MENVEO

A summary of hSBA GMTs at D30 after the 6-month vaccinations and D0 before the 12-month vaccinations in the PPAS2 is presented in Table 14.

In the PPAS2 (subjects vaccinated at Visits 1 to 3 with valid pre-4th dose serology results at Visit 5 and no exclusionary protocol deviations) at D30 after the 3rd dose of MenACYW conjugate vaccine or MENVEO at 6 months of age, the hSBA GMTs for meningococcal serogroups A, C, Y, and W were higher in Group 1a than in Group 2a for all serogroups. The hSBA GMTs were:

- for serogroup A: 24.9 in Group 1a and 16.3 in Group 2a
- for serogroup C: 365 in Group 1a and 51.4 in Group 2a
- for serogroup Y: 83.0 in Group 1a and 42.9 in Group 2a
- for serogroup W: 92.8 in Group 1a and 51.4 in Group 2a

In the PPAS2, at D0 before the 4th dose of MenACYW conjugate vaccine or MENVEO (before the 12-month vaccinations), the hSBA GMTs were higher in Group 1a than in Group 2a for all serogroups. The hSBA GMTs were:

- for serogroup A: 9.33 in Group 1a and 6.43 in Group 2a
- for serogroup C: 57.8 in Group 1a and 4.82 in Group 2a
- for serogroup Y: 42.9 in Group 1a and 10.4 in Group 2a
- for serogroup W: 57.8 in Group 1a and 9.27 in Group 2a

Table 14: Summary of geomtric means of hSBA titers at D30 after 6-month vaccinations and D0 before 12-month vaccinations for Groups 1a and 2a – Per-Protocol Analysis Set 2

		Group 1a (N=647)			Group 2a (N=329)		
Serogroup	Time Point	M	GMT	95% CI	M	GMT	95% CI
A	D30 after 3rd dose	547	24.9	(21.6 ; 28.6)	258	16.3	(13.5 ; 19.6)
	D0 before 4th dose	627	9.33	(8.45 ; 10.3)	321	6.43	(5.64 ; 7.33)
C	D30 after 3rd dose	542	365	(325 ; 411)	268	51.4	(42.9 ; 61.5)
	D0 before 4th dose	637	57.8	(51.5 ; 64.8)	324	4.82	(4.22 ; 5.50)
Y	D30 after 3rd dose	558	83.0	(75.0 ; 91.8)	270	42.9	(36.7 ; 50.0)
	D0 before 4th dose	633	42.9	(39.3 ; 46.7)	327	10.4	(9.15 ; 11.9)
W	D30 after 3rd dose	571	92.8	(84.8 ; 102)	277	51.4	(43.9 ; 60.0)
	D0 before 4th dose	644	57.8	(52.7 ; 63.3)	329	9.27	(8.15 ; 10.5)

N : number of subjects in per-protocol analysis set 2, for immunogenicity persistence evaluation
M: number of subjects with valid serology results for the particular serogroup and time point
95% CI calculated using calculation for normal distribution on log10(titer) following by antilog transformation
Group 1a: MenACYW conjugate vaccine and routine vaccines at 2, 4, 6, and 12 to 15 months of age
Group 2a: MENVEO® at 2, 4, 6, and 12 months of age and routine vaccines at 2, 4, 6, 12, and 15 to 18 months of age

hSBA Titers ≥ 1:4 and ≥ 1:8 After the 3rd Dose and Before the 4th Dose of MenACYW Conjugate Vaccine or MENVEO

In the PPAS2, at D30 after the 3rd dose of MenACYW conjugate vaccine or MENVEO at 6 months of age, the percentages of subjects with hSBA titers ≥ 1:4 and ≥ 1:8 were:

- for serogroup A: 87.0% and 77.3% in Group 1a and 84.9% and 70.2% in Group 2a
- for serogroup C: 99.3% and 99.1% in Group 1a and 93.7% and 91.0% in Group 2a
- for serogroup Y: 99.1% and 98.6% in Group 1a and 96.3% and 92.2% in Group 2a
- for serogroup W: 99.8% and 98.8% in Group 1a and 97.5% and 94.2% in Group 2a

In the PPAS2, at D0 before the 4th dose of MenACYW conjugate vaccine or MENVEO (before the 12-month vaccinations), the percentages of subjects with hSBA titers ≥ 1:4 and ≥ 1:8 were:

- for serogroup A: 82.5% and 59.0% in Group 1a and 66.4% and 47.0% in Group 2a

- for serogroup C: 95.4% and 92.9% in Group 1a and 49.1% and 34.0% in Group 2a
- for serogroup Y: 99.2% and 96.8% in Group 1a and 83.5% and 69.1% in Group 2a
- for serogroup W: 98.9% and 97.2% in Group 1a and 82.7% and 62.0% in Group 2a

Secondary Objective #4: Antibody Responses of Routine Pediatric Vaccines Administered Concomitantly With MenACYW Conjugate Vaccine or MENVEO

For all reported results comparable results were observed in the respective full analysis sets or otherwise reported here.

At D30 after the 6-month vaccinations for Groups 1 and 2 (PPAS1)

• Anti-PRP Ab

In the PPAS1, at D30 after the 6-month vaccinations, the anti-PRP Ab GMCs were comparable between both groups (7.52 in Group 1 and 6.24 in Group 2).

• Anti-diphtheria Ab

In the PPAS1, at D30 after the 6-month vaccinations, the anti-diphtheria Ab GMCs were comparable between both groups (0.880 in Group 1 and 0.830 in Group 2).

The percentages of subjects with anti-diphtheria Ab concentrations ≥ 0.01 IU/mL and ≥ 0.1 IU/mL in the PPAS1 were comparable between both groups (100% and 98.7%, respectively in Group 1, and 100% and 98.6%, respectively in Group 2).

• Anti-tetanus Ab

In the PPAS1, at D30 after the 6-month vaccinations, the anti-tetanus Ab GMCs were comparable between both groups (1.88 in Group 1 and 1.84 in Group 2).

The percentages of subjects with anti-tetanus Ab concentrations ≥ 0.01 IU/mL and ≥ 0.1 IU/mL in the PPAS1 were comparable between both groups (100% and 99.7%, respectively in Group 1 and 100% and 100%, respectively in Group 2).

• Anti-hepatitis B Ab

In the PPAS1, at D30 after the 6-month vaccinations, the anti-HB Ab GMCs were comparable between both groups (758 in Group 1 and 873 in Group 2).

The percentages of subjects with anti-HB Ab concentrations ≥ 100 mIU/mL in the PPAS1 were comparable between both groups (89.0% in Group 1 and 92.5% in Group 2).

• Anti-poliovirus (types 1, 2, and 3) Ab

In the PPAS1, at D30 after the 6-month vaccinations, the percentages of subjects with antipolio 1, 2, and 3 Ab titers ≥ 1:8 were comparable between both groups. The response rates were 100% in both groups for the 3 anti-polio types.

• Anti-rotavirus serum IgA Ab

In the PPAS1, at D30 after the 6-month vaccinations, the percentages of subjects with ≥ 4-fold rise of anti-rotavirus concentrations from baseline were comparable between both groups (88.7% in Group 1 and 91.3% in Group 2).

• Anti-pertussis (PT, FHA, PRN, and FIM) Ab

In the PPAS1, at D30 after the 6-month vaccinations, the vaccine seroresponse rates for the antigens PT, FHA, PRN, and FIM were comparable between both groups.

The percentages of subjects who reached a vaccine seroresponse were:

- For PT: 79.2% in Group 1 and 80.1% in Group 2
- For FHA: 57.2% in Group 1 and 57.3% in Group 2
- For PRN: 40.8% in Group 1 and 41.0% in Group 2
- For FIM: 69.7% in Group 1 and 66.9% in Group 2

• Anti-pneumococcal Ab (PCV13)

In the PPAS1, at D30 after the 6-month vaccinations, the GMCs were comparable between both groups, except for serotypes 1, 5, 6A, 6B, 9V, and 23F which were higher in Group 1 than in Group 2.

In the FAS1, the GMCs were higher in Group 1 than in Group 2 for all serogroups, except for serotypes 7F, 14, and 18C which were comparable between both groups.

In the PPAS1, at D30 after the 6-month vaccinations, the percentages of subjects with antipneumococcal Ab concentrations $\geq$ 0.35 μg/mL were comparable between both groups for all pneumococcal serotypes, except for serotype 6A which was higher in Group 1 than in Group 2.

The percentages of subjects with anti-pneumococcal Ab concentrations $\geq$ 1.0 μg/mL were comparable between both groups for all pneumococcal serotypes, except for serotypes 5 and 6A which were higher in Group 1 than in Group 2.

In the FAS1, the percentages of subjects with anti-pneumococcal Ab concentrations $\geq$ 0.35 μg/mL were comparable between Groups 1 and 2 for all pneumococcal serotypes.

At D30 after the 12-month vaccinations for Groups 1a and 2a (PPAS3)

• Anti-measles Ab

In the PPAS3, at D30 after the 12-month vaccinations, the anti-measles Ab GMCs were comparable between both groups (3473 in Group 1a and 3306 in Group 2a).

• Anti-mumps Ab

In the PPAS3, at D30 after the 12-month vaccinations, the anti-mumps Ab GMCs were comparable between both groups (76.9 in Group 1a and 83.7 in Group 2a).

• Anti-rubella Ab

In the PPAS3, at D30 after the 12-month vaccinations, the anti-rubella Ab GMCs were comparable between both groups (69.9 in Group 1a and 72.1 in Group 2a).

• Anti-varicella Ab

In the PPAS3, at D30 after the 12-month vaccinations, the anti-varicella Ab GMCs were comparable between both groups (13.0 in Groups 1a and 2a).

• Anti-pneumococcal Ab (PCV13)

In the PPAS3, at D30 after the 12-month vaccinations, the percentages of subjects with antipneumococcal Ab concentrations $\geq$ 0.35 μg/mL and $\geq$ 1.0 μg/mL were comparable between both groups for all the vaccine serotypes of PCV13.

At D0 before the 15-month vaccinations for Groups 1b and 2b (immune persistence, PPAS2)

• Anti-PRP Ab

In the PPAS2, the anti-PRP Ab GMCs were comparable between both groups at D30 after the 6-month vaccinations (7.01 in Group 1b and 5.44 in Group 2b) and at D0 before the 15-month vaccinations (0.728 in Group 1b and 0.888 in Group 2b).

In the PPAS2, the percentages of subjects with anti-PRP Ab concentrations ≥ 0.15 μg/mL were comparable between both groups at D30 after the 6-month vaccinations (99.2% in Group 1b and 96.2% in Group 2b) and at D0 before the 15-month vaccinations (82.9% in Group 1b and 82.5% in Group 2b).

• Anti-pertussis Ab

At D30 after the 6-month vaccinations in the PPAS2, the Ab GMCs against the PT, FHA, PRN, and FIM antigens were comparable between both groups for each antigen. The Ab GMCs were:

- For PT: 73.5 in Group 1b and 81.5 in Group 2b
- For FHA: 100 in Group 1b and 104 in Group 2b
- For PRN: 39.9 in Group 1b and 38.0 in Group 2b
- For FIM: 311 in Group 1b and 281 in Group 2b

At D0 before the 15-month vaccinations in the PPAS2, the Ab GMCs were comparable between both groups for each antigen. The Ab GMCs were:

- For PT: 11.2 in Group 1b and 12.3 in Group 2b
- For FHA: 16.5 in Group 1b and 17.4 in Group 2b
- For PRN: 8.75 in Group 1b and 9.53 in Group 2b
- For FIM: 44.8 in Group 1b and 46.0 in Group 2b

At D30 after the 15-month vaccinations for Groups 1b and 1a (PPAS3)

• Anti-PRP Ab

In the PPAS3, at D30 after the 15-month vaccinations, the anti-PRP Ab GMCs were higher in Group 2b (46.7) than in Group 1b (25.8).

• Anti-diphtheria Ab

In the PPAS3, at D30 after the 15-month vaccinations, the anti-diphtheria Ab GMCs were comparable between both groups (4.45 in Group 1b and 5.03 in Group 2b).

The percentages of subjects with anti-diphtheria Ab concentrations ≥ 0.1 IU/mL and ≥ 1.0 IU/mL were comparable between both groups (100% and 96.7%, respectively in Group 1b, and 100% and 96.8% in Group 2b).

• Anti-tetanus Ab

In the PPAS3, at D30 after the 15-month vaccinations, the anti-tetanus Ab GMCs were comparable between both groups (6.27 in Group 1b and 7.87 in Group 2b).

In the FAS3, the anti-tetanus Ab GMCs were higher in Group 2b (7.11) than in Group 1b (5.61).

The percentages of subjects with anti-tetanus Ab concentrations ≥ 0.1 IU/mL and ≥ 1.0 IU/mL were comparable between both groups (99.7% and 98.7%, respectively in Group 1b and 100% and 97.6%, respectively in Group 2b).

• Anti-poliovirus (types 1, 2, and 3) Ab

In the PPAS3, at D30 after the 15-month vaccinations, the percentages of subjects with antipolio 1, 2, and 3 Ab titers ≥ 1:8 were comparable between both groups. The response rates were 100% in both groups for all 3 anti-polio types.

• Anti-pertussis (PT, FHA, PRN, and FIM) Ab

In the PPAS3, at D30 after the 15-month vaccinations, the anti-pertussis Ab GMCs were higher in Group 2b than in Group 1b for PT and PRN and comparable between both groups for FHA and FIM. The Ab GMCs were:

- For PT: 149 in Group 1b and 206 in Group 2b
- For FHA: 135 in Group 1b and 170 in Group 2b
- For PRN: 150 in Group 1b and 240 in Group 2b
- For FIM: 669 in Group 1b and 728 in Group 2b

Overall conclusion on secondary objective #4:

Overall, antibody responses of concomitant routine pediatric vaccines administered with MenACYW conjugate vaccine or MENVEO in infants and toddlers were comparable.

Observed differences among the groups were not considered to have any clinical relevance.

Secondary Objective #5: Antibody Responses of MenACYW Conjugate Vaccine Compared to MENVEO When Administered With Concomitant Vaccines

For all reported results comparable results were observed in the respective full analysis sets or otherwise reported here.

hSBA GMTs Meningococcal Serogroups A, C, Y, and W

A summary of hSBA GMTs at D0 before the 2-month vaccinations (1st dose of MenACYW conjugate vaccine or MENVEO) and D30 after the 6-month vaccinations (3rd dose of MenACYW conjugate vaccine or MENVEO) in the PPAS1 is presented in Table 15.

In the PPAS1, at D0 before the 1st dose of MenACYW conjugate vaccine or MENVEO, the hSBA GMTs were comparable between Group 1 and Group 2 for all serogroups.

In the PPAS1, at D30 after the 3rd dose at 6 months of age, the hSBA GMTs were higher in Group 1 than in Group 2 for all serogroups.

A summary of hSBA GMTs at D0 before the 4th dose and D30 after the 4th dose of MenACYW conjugate vaccine or MENVEO in the PPAS3 is presented in Table 16.

In the PPAS3, at D0 before the 4th dose (before the 12-month vaccinations for Groups 1a and 2a and before the 15-month vaccinations for Group 1b), the hSBA GMTs were higher in Group 1a than in Group 2a for all serogroups. They were comparable between Groups 1b and 2a for serogroup A and higher in Group 1b than in Group 2a for serogroups C, Y, and W.

In the PPAS3, at D30 after the 4th dose, the hSBA GMTs were comparable between Groups 1a, 1b, and 2a for serogroup A. They were higher in Groups 1a and 1b than in Group 2a for serogroups C, Y, and W.

Table 15: Summary of geomtric means of hSBA titers at D0 before 2 months vaccinations and D30 after 6-month vaccinations during infant stage - Per-Protocol Analysis Set 1

		Group 1 (N=928)			Group 2 (N=460)		
Serogroup	Time Point	M	GMT	95% CI	M	GMT	95% CI
A	D0 before 1st dose	722	3.36	(3.20 ; 3.54)	350	3.01	(2.83 ; 3.21)
	D30 after 3rd dose	852	25.3	(22.7 ; 28.3)	409	15.1	(13.0 ; 17.5)
C	D0 before 1st dose	758	2.75	(2.59 ; 2.92)	371	2.62	(2.45 ; 2.80)
	D30 after 3rd dose	835	391	(356 ; 428)	421	53.0	(45.9 ; 61.1)
Y	D0 before 1st dose	754	2.94	(2.75 ; 3.13)	373	2.87	(2.63 ; 3.14)
	D30 after 3rd dose	861	88.1	(81.1 ; 95.7)	423	40.6	(35.8 ; 46.0)
W	D0 before 1st dose	774	2.87	(2.70 ; 3.05)	385	2.64	(2.47 ; 2.83)
	D30 after 3rd dose	883	98.1	(91.1 ; 106)	438	48.7	(43.1 ; 55.1)

N: number of subjects in per-protocol analysis set 1, for infant vaccinations
M: number of subjects with valid serology results for the particular serogroup and time point
95% CI calculated using calculation for normal distribution on log10(titer) following by antilog transformation
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines
Group 2: MENVEO® and routine pediatric vaccines

Table 16: Summary of geometric means of hSBA titers at D0 before the 4th dose and D30 after the 4th dose – Per-Protocol Analysis Set 3

		Group 1a (N=675)			Group 1b (N=308)			Group 2a (N=308)		
Serogroup	Time Point	M	GMT	95% CI	M	GMT	95% CI	M	GMT	95% CI
A	D0 before 4th dose	607	10.6	(9.54 ; 11.8)	272	8.02	(7.02 ; 9.16)	282	6.64	(5.74 ; 7.68)
	D30 after 4th dose	642	67.1	(58.1 ; 77.5)	283	78.0	(64.4 ; 94.5)	296	56.9	(46.7 ; 69.5)
C	D0 before 4th dose	612	61.3	(54.4 ; 69.0)	282	41.3	(34.2 ; 49.9)	284	4.45	(3.91 ; 5.08)
	D30 after 4th dose	655	678	(606 ; 758)	292	654	(555 ; 770)	300	90.9	(75.7 ; 109)
Y	D0 before 4th dose	611	43.5	(39.7 ; 47.6)	283	42.4	(37.1 ; 48.5)	287	9.97	(8.72 ; 11.4)
	D30 after 4th dose	651	296	(268 ; 327)	295	369	(321 ; 425)	295	186	(158 ; 219)
W	D0 before 4th dose	619	57.9	(52.7 ; 63.7)	282	57.7	(49.7 ; 67.0)	288	9.02	(7.88 ; 10.3)
	D30 after 4th dose	651	387	(352 ; 426)	289	823	(693 ; 977)	305	175	(149 ; 206)

N: number of subjects in per-protocol analysis set 3, for 2nd year of life vaccinations
M: number of subjects with valid serology results for the particular serogroup and time point
95% CI calculated using calculation for normal distribution on log10(titer) following by antilog transformation
Group 1a: MenACYW conjugate vaccine and routine vaccines at 2, 4, 6, and 12 to 15 months of age
Group 1b: MenACYW conjugate vaccine at 2, 4, 6, and 15 to18 months of age and routine vaccines at 2, 4, 6, 12 to 15 months of age
Group 2a: MENVEO® at 2, 4, 6, and 12 months of age and routine vaccines at 2, 4, 6, 12, and 15 to 18 months of age

hSBA Ab Titers Distribution and RCDC

In the PPAS1, at D30 after the 6-month vaccinations, the percentages of subjects with hSBA titers ≥ 1:4 and ≥ 1:256 were increased compared to D0 before the 3rd dose in both groups and for all serogroups.

The Ab distributions for serogroups A, Y, and W were comparable between both groups and were shifted to the right in Group 1 as compared to Group 2 for serogroup C.

In the PPAS3, at D30 after the 4th dose of MenACYW conjugate vaccine or MENVEO, the percentages of subjects with hSBA titer ≥ 1:4 and ≥ 1:256 were increased compared to 30 days before the 4th dose in all groups and for all serogroups.

The Ab distributions for serogroups A, Y and W were comparable between Groups 1a and 2a and were shifted to the right in Group 1a as compared to Group 2a for serogroup C. The Ab distributions were comparable for all serogroups between Groups 1a and 1b.

hSBA Antibody Titers ≥ 1:4 and ≥ 1:8

In the PPAS1, at D30 after the 3rd dose of MenACYW conjugate vaccine or MENVEO at 6 months of age, the percentages of subjects with hSBA titers ≥ 1:4 and ≥ 1:8 were:

- For serogroup A: 87.8% and 77.9% in Group 1 and 83.1% and 67.7% in Group 2
- For serogroup C: 99.3% and 99.0% in Group 1 and 94.3% and 91.2% in Group 2
- For serogroup Y: 99.1% and 98.3% in Group 1 and 96.2% and 91.7% in Group 2
- For serogroup W: 99.5% and 98.6% in Group 1 and 97.0% and 92.9% in Group 2

In the PPAS3, at D30 after the 4th dose of MenACYW conjugate vaccine or MENVEO, the percentages of subjects with hSBA titers ≥ 1:4 and ≥ 1:8 were:

- For serogroup A: 91.4% and 87.7% in Group 1a and 96.8% and 92.6% in Group 1b, and 93.6% and 88.2% in Group 2a, respectively
- For serogroup C: 99.5% and 99.4% in Group 1a, 99.7% and 99.3% in Group 1b, and 96.0% and 93.3% in Group 2a, respectively
- For serogroup Y: 99.5% and 99.1% in Group 1a, 99.3% and 99.3% in Group 1b, and 99.0% and 98.6% in Group 2a, respectively
- For serogroup W: 99.5% and 99.4% in Group 1a, 100% and 100% in Group 1b, and 99.0% and 99.0% in Group 2a, respectively

hSBA Antibody Titer ≥ 4-Fold Rise From Pre- to Post-vaccination

In the PPAS1, the percentages of subjects with ≥ 4-fold rise of hSBA titer from pre-1st dose to post-3rd dose at 6 months of age were higher in Group 1 than in Group 2 for all serogroups. The percentages of subjects with a ≥ 4-fold rise of hSBA titer were:

- For serogroup A: 64.4% in Group 1 and 50.6% in Group 2
- For serogroup C: 96.4% in Group 1 and 82.8% in Group 2
- For serogroup Y: 88.7% in Group 1 and 81.8% in Group 2
- For serogroup W: 92.8% in Group 1 and 85.6% in Group 2

In the PPAS3, the percentages of subjects with ≥ 4-fold rise of hSBA titer from pre-4th dose to post-4th dose (12-month vaccinations for Groups 1a and 2a and 15-month vaccinations for Group 1b) were comparable between Groups 1a, 1b, and 2a for serogroups A and C, higher in Group 2a than in Groups 1a and 1b for serogroup Y, and higher in Group 2a than in Group 1a and comparable between Groups 1b and 2a for serogroup W. The percentages of subjects with a ≥ 4-fold rise of hSBA titer were:

- For serogroup A: 66.3% in Group 1a, 75.0% in Group 1b, and 73.2% in Group 2a
- For serogroup C: 90.3% in Group 1a, 90.8% in Group 1b, and 87.1% in Group 2a
- For serogroup Y: 80.2% in Group 1a, 83.1% in Group 1b, and 93.1% in Group 2a
- For serogroup W: 80.4% in Group 1a, 90.3% in Group 1b, and 91.9% in Group 2a

hSBA Seroresponse

In the PPAS1, the hSBA vaccine seroresponse rates correspond to the percentages of subjects with 4-fold rise of hSBA titers. These data are already described above.

The number and percentage of subjects with hSBA vaccine seroresponse at D30 post-4th dose (at the 12-month vaccinations for Groups 1a and 2a and at the 15-month vaccinations for Group 1b) in the PPAS3 are presented in Table 18.

At D30 post-4th dose in the PPAS3, the percentages of subjects with hSBA seroresponse were comparable between Groups 1a, 1b, and 2a for serogroups A and W, higher in Groups 1a and 1b than in Group 2a for serogroup C, comparable between Groups 1a and 2a for serogroup Y, and higher in Group 1b than in Group 2a for serogroup Y. The percentages of subjects with hSBA seroresponse were:

- For serogroup A: 79.4% in Group 1a, 84.3% in Group 1b, and 77.6% in Group 2a
- For serogroup C: 97.0% in Group 1a, 97.9% in Group 1b, and 88.2% in Group 2a
- For serogroup Y: 96.4% in Group 1a, 98.3% in Group 1b, and 92.3% in Group 2a
- For serogroup W: 97.6% in Group 1a, 98.8% in Group 1b, and 96.4% in Group 2a

Table 17: Summary of hSBA vaccine seroreonse at D30 post-3rd dose vaccinations during infant stage – Per-Protocol Analysis Set 1

	Group 1 (N=928)			Group 2 (N=460)		
Serogroup	n/M	%	95% CI	n/M	%	95% CI
A	439/682	64.4	(60.6 ; 68.0)	163/322	50.6	(45.0 ; 56.2)
C	666/691	96.4	(94.7 ; 97.6)	280/338	82.8	(78.4 ; 86.7)
Y	622/701	88.7	(86.2 ; 91.0)	284/347	81.8	(77.4 ; 85.8)
W	686/739	92.8	(90.7 ; 94.6)	316/369	85.6	(81.6 ; 89.1)

N: number of subjects in per-protocol analysis set 1, for infant vaccinations
M: number of subjects with valid serology results for the particular serogroup and timepoint
Percentages are based on M.
n: number of subjects experiencing the endpoint listed in the first column and met the criterion
95% CI of the single proportion calculated from the exact binomial method.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines
Group 2: MENVEO® and routine pediatric vaccines

Table 18: Summary of hSBA vaccine seroreonse at D30 post-4th dose vaccinations during 2nd year of life – Per-Protocol Analysis Set 3

	Group 1a (N=675)			Group 1b (N=308)			Group 2a (N=308)		
Serogroup	n/M	%	95% CI	n/M	%	95% CI	n/M	%	95% CI
A	398/501	79.4	(75.6 ; 82.9)	188/223	84.3	(78.9 ; 88.8)	173/223	77.6	(71.5 ; 82.9)
C	514/530	97.0	(95.1 ; 98.3)	235/240	97.9	(95.2 ; 99.3)	210/238	88.2	(83.4 ; 92.0)
Y	504/523	96.4	(94.4 ; 97.8)	233/237	98.3	(95.7 ; 99.5)	215/233	92.3	(88.1 ; 95.4)
W	527/540	97.6	(95.9 ; 98.7)	239/242	98.8	(96.4 ; 99.7)	241/250	96.4	(93.3 ; 98.3)

N: number of subjects in per-protocol analysis set 3, for 2nd year of life vaccinations; M: number of subjects with valid serology results for the particular serogroup and time point
n: number of subjects experiencing the endpoint listed in the first column and met the criterion
hSBA vaccine seroresponse for serogroups A, C, Y and W is defined as: for a subject with a pre-vaccination titer < 1:8.
Post-4th dose vaccinations titer must be >= 1:16; for a subject with a pre-vaccination titer >= 1:8.
Group 1a: MenACYW conjugate vaccine and routine vaccines at 2, 4, 6, and 12 to 15 months of age
Group 1b: MenACYW conjugate vaccine at 2, 4, 6, and 15 to18 months of age and routine vaccines at 2, 4, 6, 12 to 15 months of age
Group 2a: MENVEO® at 2, 4, 6, and 12 months of age and routine vaccines at 2, 4, 6, 12, and 15 to 18 months of age

Secondary Objective #6: Antibody Responses after the 4th Dose of MenACYW Conjugate Vaccine Administered at 12 or 15 Months of Age

For all reported results comparable results were observed in the respective full analysis sets or otherwise reported here.

hSBA GMTs Meningococcal Serogroups A, C, Y, and W

A summary of hSBA GMTs at D30 after the 3rd dose and D0 before the 4th dose of MenACYW conjugate vaccine at the 12-month vaccinations (Group 1a) and at the 15-month vaccinations (Group 1b) in the PPAS2 is presented in Table 19.

In the PPAS2, at D30 after the 3rd dose of MenACYW conjugate vaccine at 6 months of age, the hSBA titers were comparable between Groups 1a and 1b for all serogroups.

In the PPAS2, at D0 before the 4th dose of MenACYW conjugate vaccine (at the 12-month vaccinations in the Group 1a and at the 15-month vaccinations in the Group 1b), the hSBA titers were comparable between Groups 1a and 1b for serogroups A, Y, and W, and higher in Group 1a than in Group 1b for serogroup C.

A summary of hSBA GMTs after the 4th dose of MenACYW conjugate vaccine at 12-month vaccinations in Group 1a and at the 15-month vaccinations in Group 1b in the PPAS3 is presented in Table 20.

At D30 after the 4th dose in the PPAS3, the hSBA GMTs Group 1b/Group 1a ratios was 1.25 and 2.13 for serogroups Y and W, respectively, with lower bound of the 95% CI greater than 1.0.

There is no clinical relevance of this finding. For serogroups A and C, the ratios were 1.16 and 0.965, respectively.

Table 19: Summary of geometric means of hSBA titers at D30 after 3rd dose and D0 before 4th dose – Per-Protocol Analysis Set 2

		Group 1a (N=647)			Group 1b (N=295)		
Serogroup	**Time Point**	**M**	**GMT**	**95% CI**	**M**	**GMT**	**95% CI**
A	D30 after 3rd dose	547	24.9	(21.6 ; 28.6)	257	23.3	(19.1 ; 28.3)
	D0 before 4th dose	627	9.33	(8.45 ; 10.3)	283	7.90	(6.95 ; 8.99)
C	D30 after 3rd dose	542	365	(325 ; 411)	253	387	(329 ; 455)
	D0 before 4th dose	637	57.8	(51.5 ; 64.8)	294	36.8	(30.5 ; 44.4)
Y	D30 after 3rd dose	558	83.0	(75.0 ; 91.8)	260	83.3	(71.9 ; 96.6)
	D0 before 4th dose	633	42.9	(39.3 ; 46.7)	295	43.6	(38.1 ; 50.0)
W	D30 after 3rd dose	571	92.8	(84.8 ; 102)	269	96.9	(83.8 ; 112)
	D0 before 4th dose	644	57.8	(52.7 ; 63.3)	295	55.6	(48.1 ; 64.3)

N: number of subjects in per-protocol analysis set 2, for immunogenicity persistence evaluation
M: number of subjects with valid serology results for the particular serogroup and time point
n: number of subjects experiencing the endpoint listed in the first 2 columns
95% CI calculated using calculation for normal distribution on log10(titer) following by antilog transformation
Group 1a: MenACYW conjugate vaccine and routine vaccines at 2, 4, 6, and 12 to 15 months of age
Group 1b: MenACYW conjugate vaccine at 2, 4, 6, and 15 to18 months of age and routine vaccines at 2, 4, 6, 12 to 15 months of age

Table 20: Summary of geometric means of hSBA titers after 4th dose vaccinations during 2nd year of life – Per-Protocol Analysis Set 3

	Group 1a (N=675)			Group 1b (N=308)			Group 1b / Group 1a	
Serogroup	**M**	**GMT**	**95% CI**	**M**	**GMT**	**95% CI**	**GMT Ratio**	**95% CI**
A	642	67.1	(58.1 ; 77.5)	283	78.0	(64.4 ; 94.5)	1.16	(0.915 ; 1.48)
C	655	678	(606 ; 758)	292	654	(555 ; 770)	0.965	(0.790 ; 1.18)
Y	651	296	(268 ; 327)	295	369	(321 ; 425)	1.25	(1.05 ; 1.49)
W	651	387	(352 ; 426)	289	823	(693 ; 977)	2.13	(1.75 ; 2.59)

N: number of subjects in per-protocol analysis set 3, for 2nd year of life vaccinations
M: number of subjects with valid serology results for the particular serogroup and time point
n: number of subjects experiencing the endpoint listed in the first 2 columns
Group 1a: MenACYW conjugate vaccine and routine vaccines at 2, 4, 6, and 12 to 15 months of age
Group 1b: MenACYW conjugate vaccine at 2, 4, 6, and 15 to18 months of age and routine vaccines at 2, 4, 6, 12 to 15 months of age

hSBA Antibody Titers ≥ 1:4 and ≥ 1:8

The differences in the proportion of subjects with an hSBA titer ≥ 1:4 between Group 1b and Group 1a ranged from -0.22% to 0.46% for serogroups C, Y and W. For serogroup A, the observed difference (Group 1b - Group 1a) was equal to 5.39% with the lower limit of the 95% CI greater than 0.

The differences in the proportion of subjects with an hSBA titer ≥ 1:8 between Group 1b and Group 1a ranged from -0.07% and 0.61% for serogroups C, Y and W. For serogroup A, the observed difference (Group 1b - Group 1a) was equal to 4.88% with the lower limit of the 95% CI greater than 0.

hSBA Antibody Titer ≥ 4-Fold Rise From Pre- to Post-vaccination

In the PPAS3, the percentages of subjects with ≥ 4-fold rise of hSBA titer from pre-1st dose to post-4th dose vaccinations were comparable between Groups 1a and 1b for all serogroups:

- For serogroup A: 79.4% in Group 1a and 84.3% in Group 1b
- For serogroup C: 97.0% in Group 1a and 97.9% in Group 1b
- For serogroup Y: 96.4% in Group 1a and 98.3% in Group 1b
- For serogroup W: 97.6% in Group 1a and 98.8% in Group 1b

In the PPAS3, the percentages of subjects with ≥ 4-fold rise of hSBA titer from pre-4th dose to post-4th dose vaccinations were comparable between Groups 1a and 1b for serogroups A, C, and Y, and higher in Group 1b than in Group 1a for serogroup W. The percentages of subjects with a ≥ 4-fold rise of hSBA titer were:

- For serogroup A: 66.3% in Group 1a and 75.0% in Group 1b
- For serogroup C: 90.3% in Group 1a and 90.8% in Group 1b
- For serogroup Y: 80.2% in Group 1a and 83.1% in Group 1b
- For serogroup W: 80.4% in Group 1a and 90.3% in Group 1b

hSBA Seroresponse

In the PPAS3, the hSBA vaccine seroresponse rates correspond to the percentages of subjects with 4-fold rise of hSBA titers. These data are already described above.

The differences in the vaccine seroresponse rates (Group 1b - Group 1a) ranged from 0.94% to 4.86%. For all serogroups, the 95% CIs of the difference in the percentage included 0.

Table 21: Summary of hSBA vaccine seroresonse rate at D30 after the 4th dose vaccinations during 2nd year of life – Per-Protocol Analysis set 3

	Group 1a (N=675)			Group 1b (N=308)			Group 1b - Group 1a	
Serogroup	n/M	%	95% CI	n/M	%	95% CI	Difference (%)	95% CI
A	398/501	79.4	(75.6 ; 82.9)	188/223	84.3	(78.9 ; 88.8)	4.86	(-1.43 ; 10.49)
C	514/530	97.0	(95.1 ; 98.3)	235/240	97.9	(95.2 ; 99.3)	0.94	(-2.00 ; 3.12)
Y	504/523	96.4	(94.4 ; 97.8)	233/237	98.3	(95.7 ; 99.5)	1.95	(-0.93 ; 4.17)
W	527/540	97.6	(95.9 ; 98.7)	239/242	98.8	(96.4 ; 99.7)	1.17	(-1.38 ; 3.02)

N: number of subjects in per-protocol analysis set 3, for 2nd year of life vaccinations
M: number of subjects with valid serology results for the particular serogroup and time point; Percentages are based on M.
n: number of subjects experiencing the endpoint listed in the first column and met the criterion
hSBA vaccine seroresponse for serogroups A, C, Y and W is defined as: for a subject with a pre-1st dose vaccinations titer < 1:8.
Post-4th dose vaccinations titer must be >= 1:16; for a subject with a pre-1st dose vaccinations titer >= 1:8.
Post-4th dose vaccinations titer must be at least 4-fold greater than the pre-1st dose vaccinations titer.
Group 1a: MenACYW conjugate vaccine and routine vaccines at 2, 4, 6, and 12 to 15 months of age
Group 1b: MenACYW conjugate vaccine at 2, 4, 6, and 15 to18 months of age and routine vaccines at 2, 4, 6, 12 to 15 months of age

Safety results

Safety data were collected as follows:

- immediate unsolicited systemic AEs within 30 minutes of each vaccination,
- solicited AEs from D0 to D07 after each vaccination,
- unsolicited AEs from D0 to D30 after each vaccination and
- SAE (including AESIs and MAAEs) throughout the study from Visit 1 until the end of the 6-month follow-up period after the last vaccination.

Overall population (overall SafAS)

In the overall SafAS after any vaccination, there were 1 subject (< 0.1%) in Group 1 (infantile spitting up) and 1 subject (0.1%) in Group 2 (rash) with at least 1 immediate unsolicited AE within 30 minutes of any vaccination. None were assessed as related to study vaccine by the Investigator in any group.

Solicited reactions

The proportion of subjects who experienced at least 1 solicited injection site reaction after any vaccination was 78.0% in Group 1 and 79.8% in Group 2. After any vaccination with MenACYW conjugate vaccine or MENVEO, there were 71.7% of subjects in Group 1 and 71.0% of subjects in

Group 2 with at least 1 solicited injection site reaction. The proportion of subjects with at least 1 solicited systemic reaction was 80.0% in Group 1 and 81.9% in Group 2.

For MenACYW conjugate vaccine or MENVEO, tenderness was the most frequently reported solicited injection site reaction within 7 days following injection in both groups, with 67.2% and 67.6% of subjects in Group 1 and Group 2, respectively. Erythema and swelling were reactions less frequently experienced:

- Erythema in 33.2% of subjects in Group 1 and 33.1% of subjects in Group 2
- Swelling in 24.5% of subjects in Group 1 and 23.4% of subjects in Group 2

In both groups, most solicited injection site reactions started within D0 to D3 and resolved (spontaneously) after 1-3 days. Solicited injection site reactions ongoing at D8 were tenderness (4 and 2 subjects in Group 1 and Group 2, respectively), erythema (4 and 2 subjects in Group 1 and Group 2, respectively), and swelling (2 and 4 subjects in Group 1 and Group 2, respectively).

Most solicited injection site reactions were of Grade 1 or 2 intensity. For MenACYW conjugate vaccine or MENVEO, a total of 154 subjects (9.4%) in Group 1 and 75 subjects (9.0%) in Group 2 experienced at least 1 Grade 3 solicited injection site reaction. Grade 3 solicited injection site reactions consisted of tenderness reported in 149 subjects (9.1%) and 72 subjects (8.7%) in Group 1 and Group 2, respectively. For all study vaccines, a total of 328 subjects experienced at least 1 Grade 3 solicited injection site reaction within 7 days of vaccination: 212 subjects (12.9%) in Group 1 and 116 subjects (14.0%) in Group 2, respectively. Grade 3 solicited injection site reactions predominantly consisted of tenderness in both groups.

Irritability was the most frequently reported solicited systemic reaction within 7 days following injection in both groups, with 70.3% and 71.8% of subjects in Group 1 and Group 2, respectively. Crying abnormal, drowsiness, appetite lost, fever, and vomiting were reactions less frequently experienced:

- Crying abnormal in 62.4% and 65.0% of subjects in Group 1 and Group 2, respectively.
- Drowsiness in 59.4% and 61.1% of subjects in Group 1 and Group 2, respectively.
- Appetite lost in 42.9% and 46.3% of subjects in Group 1 and Group 2, respectively.
- Fever in 33.4% and 35.2% of subjects in Group 1 and Group 2, respectively.
- Vomiting in 24.1% and 22.3% of subjects in Group 1 and Group 2, respectively.

In both groups, most solicited systemic reactions started within D0 to D3 and resolved (spontaneously) after 1-3 days. Solicited systemic reactions ongoing at D8 were fever (24 subjects in Group 1 and 14 subjects in Group 2), vomiting (16 subjects in Group 1 and 8 subjects in Group 2), crying abnormal (42 subjects in Group 1 and 23 subjects in Group 2), drowsiness (21 subjects in Group 1 and 17 subjects in Group 2), appetite lost (25 subjects in Group 1 and 12 subjects in Group 2), and irritability (51 subjects in Group 1 and 33 subjects in Group 2).

Most solicited systemic reactions were of Grade 1 or 2 intensity. A total of 449 subjects experienced at least 1 Grade 3 solicited systemic reaction within 7 days of any vaccination: 300 subjects (18.3%) in Group 1 and 149 subjects (17.9%) in Group 2. Grade 3 solicited systemic reactions predominantly consisted of irritability which was reported in 194 subjects (11.8%) and 95 subjects (11.4%) in Group 1 and Group 2, respectively.

Unsolicited AEs

The proportion of subjects with at least 1 unsolicited AE after any vaccination was 53.9% in Group 1 and 53.9% in Group 2. There were 5.4% of subjects in Group 1 and 6.3% of subjects in Group 2 with

at least 1 unsolicited adverse reaction (AR). After any vaccination with MenACYW conjugate vaccine or MENVEO, the proportion of subjects with at least 1 unsolicited non-serious injection site AR was 5.0% in Group 1 and 5.5% in Group 2.

Unsolicited AEs within 30 days of any vaccination (% of subjects, more than 2% of subjects per group) were mainly reported in the following SOCs:

- "Infections and infestations": 34.6% of in Group 1 and 35.2% in Group 2
- "General disorders and administration site conditions": 16.9% in Group 1 and 17.9% in Group 2
- "Gastrointestinal disorders": 17.5% in Group 1 and 17.6% in Group 2
- "Skin and subcutaneous tissue disorders": 11.2% in Group 1 and 12.9% in Group 2
- "Respiratory, thoracic and mediastinal disorders": 10.5% in both groups
- "Congenital, familial and genetic disorders": 2.7% of subjects in Group 2
- "Injury, poisoning and procedural complications": 2.4% in Group 1 and 2.5% in Group 2

Subjects (% of subjects, more than 2% of subjects per group) most frequently experienced:

- Upper respiratory tract infection: 12.4% in Group 1 and 15.0% in Group 2
- Injection site bruising: 10.7% in Group 1 and 10.1% in Group 2
- Teething: 6.1% in Group 1 and 7.2% in Group 2
- Pyrexia: 5.7% in Group 1 and 6.7% in Group 2
- Nasopharyngitis: 5.6% in Group 1 and 5.8% Group 2
- Otitis media: 4.6% in Group 1 and 5.5% in Group 2
- Cough: 4.6% in Group 1 and 4.8% in Group 2
- Diarrhea: 3.8% in Group 1 and 4.7% in Group 2
- Otitis media acute: 4.5% in Group 1 and 4.4% in Group 2
- Nasal congestion: 3.5% in both groups
- Dermatitis diaper: 2.5% in Group 1 and 3.3% in Group 2
- Bronchiolitis: 3.0% in Group 1 and 3.0% in Group 2
- Constipation: 2.7% in Group 1 and 2.9% in Group 2
- Conjunctivitis: 2.2% in Group 1 and 2.8% in Group 2
- Rash: 2.4% Group 1 and 2.7% in Group 2
- Rhinorrhea: 2.2% in Group 1 and 2.5% in Group 2
- Gastroesophageal reflux disease: 2.2% in Group 1 and 2.4% in Group 2
- Vomiting: 2.3% in Group 1 and 2.1% in Group 2
- Viral upper respiratory tract infection: 2.1% in Group 2

In both groups, most unsolicited AEs started during the time period D0 to D3 or ≥ D15 and resolved after 8 days or more. At least 1 Grade 3 unsolicited AE was reported in 4.2% of subjects in Group 1 and 3.9% of subjects in Group 2.

Grade 3 unsolicited AEs within 30 days after any vaccine injections consisted mainly of:

- Pyrexia: 18 subjects (1.0%; 19 events) in Group 1 and 8 subjects (0.9%; 8 events) in Group 2
- Injection site bruising: 7 subjects (0.4%; 10 events) in Group 1 and 4 subjects (0.5%; 4 events) in Group 2
- Respiratory syncytial virus bronchiolitis: 5 subjects (0.3%; 5 events) in Group 1 and no subject in Group 2
- Pneumonia: 3 subjects (0.2%; 3 events) in Group 1 and 2 subjects (0.2%; 2 events) in Group 2
- Respiratory syncytial virus infection: 3 subjects (0.2%; 3 events) in Group 1 and 2 subjects (0.2%; 2 events) in Group 2
- Toothache: 4 subjects (0.2%; 4 events) in Group 1 and 1 subject (0.1%; 1 event) in Group 2
- Nasopharyngitis: 1 subject (< 0.1%; 1 event) in Group 1 and 3 subjects (0.3%; 3 events) in Group 2

Discontinuation due to AE

Within 30 days of any vaccination, 1 subject (0.1%; cardiac arrest) in Group 1 and 1 subject (0.1%; congenital absence of bile ducts) in Group 2 were discontinued from the study due to 1 AE.

Serious AEs including AESIs and MAAEs

Within 30 days of any vaccination, there were 39 subjects (2.3%) in Group 1 and 11 subjects (1.3%) in Group 2 who experienced at least 1 SAE. There were 3 subjects (0.2%) in Group 1 and no subject in Group 2 with at least 1 AESI, and 689 subjects (39.9%) in Group 1 and 368 subjects (42.4%) in Group 2 with at least 1 MAAE.

During the study including the 6-month follow-up period, there were 99 subjects (5.7%) in Group 1 and 38 subjects (4.4%) in Group 2 with at least 1 SAE. There were 13 subjects (0.8%) in Group 1 and 5 subjects (0.6%) in Group 2 with at least 1 AESI, and 1050 subjects (60.8%) in Group 1 and 526 subjects (60.7%) in Group 2 with at least 1 MAAE.

SAEs reported were:

• in Group 1:

o Bronchiolitis (16 cases)

o Febrile convulsion (11 cases)

o Respiratory syncytial virus bronchiolitis (9 cases)

o Respiratory syncytial virus infection (7 cases)

o Pneumonia (6 cases)

o Influenza (5 cases)

o Seizure and respiratory distress (4 cases each)

o Pyelonephritis, parainfluenza virus infection, skull fracture, and dehydration (3 cases each)

o Croup infectious, gastroenteritis, pneumonia viral, pyelonephritis acute, upper respiratory tract infection, urinary tract infection, acute respiratory failure, respiratory failure, subdural hematoma, gastroesophageal reflux disease, and vomiting (2 cases each)

o Adenovirus infection, bacterial pyelonephritis, Bordetella infection, COVID-19, eczema coxsackie, *Escherichia* urinary tract infection, exanthema subitum, gastroenteritis norovirus, gastroenteritis viral, gastrointestinal viral infection, impetigo, otitis media, otitis media acute, perirectal abscess, pharyngitis, pharyngitis streptococcal, pneumonia mycoplasmal, rhinovirus infection, roseola, sepsis, skin bacterial infection, systemic infection, systemic viral infection, viral infection, infantile spasms, seizure like phenomena, subarachnoid hemorrhage, aspiration, hypoxia, craniocerebral injury, femur fracture, head injury, skull fractured base, upper limb fracture, abdominal pain, dysphagia, Sandifer's syndrome, pyloric stenosis, talipes, urachal abnormality, cardiac arrest, pyrexia, glioma, and hydronephrosis (1 case each)

• in Group 2:

o Respiratory syncytial virus infection (6 cases)

o Bronchiolitis, respiratory syncytial virus bronchiolitis, urinary tract infection, febrile convulsion, and dehydration (4 cases each)

o Gastroenteritis and respiratory distress (3 cases each)

o Pneumonia (2 cases)

o Influenza, COVID-19, otitis media acute, pneumonia mycoplasmal, viral infection, abscess neck, bacteremia, cellulitis, staphylococcal scalded skin syndrome, seizure, epilepsy, acute respiratory failure, apnea, post-vaccination fever, constipation, congenital absence of bile ducts, ketoacidosis, type 1 diabetes mellitus, and coagulopathy (1 case each)

Within 30 days of any vaccination, there were 39 subjects (2.3%) with 49 SAEs in Group 1 and 11 subjects (1.3%) with 15 SAEs in Group 2. SAEs reported were:

• in Group 1:

o Respiratory syncytial virus bronchiolitis (5 cases)

o Pneumonia (4 cases)

o Bronchiolitis, respiratory syncytial virus infection, and skull fracture (3 cases each)

o Pyelonephritis acute, influenza, febrile convulsion, and respiratory distress (2 cases each)

o Bacterial pyelonephritis, gastroenteritis, gastroenteritis viral, gastrointestinal viral infection, parainfluenza virus infection, pharyngitis, pneumonia viral, pyelonephritis, rhinovirus infection, systemic infection, urinary tract infection, craniocerebral injury, femur fracture, skull fractured base, upper limb fracture, seizure, subarachnoid hemorrhage, acute respiratory failure, aspiration, cardiac arrest, pyloric stenosis, vomiting, and dehydration (1 case each)

• in Group 2:

o Pneumonia and respiratory syncytial virus infection (2 cases each)

o Bronchiolitis, abscess neck, bacteremia, cellulitis, staphylococcal scalded skin syndrome, post-vaccination fever, respiratory distress, apnea, congenital absence of bile ducts, constipation, and coagulopathy (1 case each)

A total of 2 SAEs were assessed as related to study vaccine during the study including the 6-month follow-up period: 1 case of febrile convulsions reported for 1 subject (< 0.1%) in Group 1 (assessed as related to study vaccine by the Investigator and as unrelated to study vaccine by the Sponsor. See below for further details) and 1 case of post-vaccination fever reported for 1 subject (0.1%) in Group 2 (assessed as related to study vaccine by both the Investigator and the Sponsor). Both cases occurred within 30 days of vaccination.

Narratives

- One subject in Group 1b (full-term birth status) experienced a Grade 3 febrile convulsions. The event started 13 days after the 15-month vaccinations (4th dose of MenACYW conjugate vaccine administered concomitantly with Pentacel and HAVRIX), required health care contact and medication and resolved the same day. The event did not lead to study discontinuation. The event was reported with 3 concomitant non study vaccine related events: Grade 1 otitis media right ear, Grade 1 bronchiolitis and pyrexia. The subject experienced a total of 4 events of febrile convulsions, all of Grade 3 while enrolled in the study. Only the 3rd episode was reported by the Investigator as related to the investigational vaccine administered concomitantly with routine pediatric vaccines; however, the event likely may have been related to acute concomitant infections (otitis media and bronchiolitis), and therefore was assessed as unrelated to study vaccine by the Sponsor. The event was reported as an AESI.
- One subject in Group 2b (full-term birth status) experienced a Grade 2 pyrexia which was reported by the Investigator as post-vaccinations fever. The event started 8 hours following the 2-month vaccinations (1st dose of MENVEO administered concomitantly with Pentacel, Prevnar 13, RotaTeq, and ENGERIX-B), required hospitalization and resolved 3 days later. The event did not lead to study discontinuation. The event was neither an AESI nor a MAAE.

One death occurred during the study, including the 6-month follow-up period. A cardiac arrest with fatal outcome was reported for 1 infant in Group 1 (full-term birth status) 6 days after the 2-month vaccinations (1st dose of MenACYW conjugate vaccine administered concomitantly with Pentacel, Prevnar 13, RotaTeq, and ENGERIX B). This event was assessed as unrelated to the investigational vaccine administered concomitantly with routine pediatric vaccines. The event was neither an AESI nor a MAAE. The subject was discontinued from the trial due to the SAE.

Subjects aged 2 months (SafAS1) - 1st dose of MenACYW conjugate vaccine or MENVEO

No immediate unsolicited AEs were reported within 30 minutes of the 2-month vaccinations in any group.

Solicited reactions

The proportion of subjects with at least 1 solicited injection site reaction was 58.1% in Group 1 and 55.3% in Group 2. After the 1st dose of MenACYW conjugate vaccine or MENVEO, there were 49.7% of subjects in Group 1 and 46.5% of subjects in Group 2 with at least 1 solicited injection site reaction. The proportion of subjects with at least 1 solicited systemic reaction was 64.8% in Group 1 and 63.3% in Group 2.

Unsolicited AEs

The proportion of subjects with at least 1 unsolicited AE was 21.9% in Group 1 and 23.0% in Group 2. There were 1.9% of subjects in Group 1 and 2.2% of subjects in Group 2 with at least 1 unsolicited AR. After the 1st dose of MenACYW conjugate vaccine or MENVEO, the proportion of subjects who experienced at least 1 unsolicited non-serious injection site AR was 1.8% in both groups.

Discontinuation due to AEs

Within 30 days of the 2-month vaccinations, 1 subject (0.1%; cardiac arrest with fatal outcomes) in Group 1 was discontinued from the study due to 1 AE. This event was reported as an SAE and assessed as unrelated to study vaccine. No discontinuation due to AEs was reported in Group 2.

Serious AEs including AESIs and MAAEs

Within 30 days of the 2-month vaccinations, there were 10 subjects (0.6%) in Group 1 and 5 subjects (0.6%) in Group 2 with at least 1 SAE. No AESIs were reported in any group. There were 236 subjects (13.7%) in Group 1 and 134 subjects (15.5%) in Group 2 with at least 1 MAAE.

During the study including the 6-month follow-up period, there were 30 subjects (1.7%) in Group 1 and 11 subjects (1.3%) in Group 2 with at least 1 SAE, 2 subjects (0.1%) in Group 1 and no subject in Group 2 with at least 1 AESI, and 468 subjects (27.1%) in Group 1 and 250 subjects (28.8%) in Group 2 with at least 1 MAAE.

Subjects aged 4 months (SafAS2) - 2nd dose of MenACYW conjugate vaccine or MENVEO

One subject (0.1%) in Group 1 experienced 1 immediate unsolicited AE within 30 minutes of the 4-month vaccinations (infantile spitting up) which was assessed as unrelated to study vaccine by the Investigator. No subject in Group 2 experienced an immediate unsolicited AE.

Solicited reactions

The proportion of subjects who experienced at least 1 solicited injection site reaction was 57.6% in Group 1 and 58.0% in Group 2. After the 2nd dose of MenACYW conjugate vaccine or MENVEO, there were 48.4% of subjects in Group 1 and 48.3% of subjects in Group 2 with at least 1 solicited injection site reaction. The proportion of subjects with at least 1 solicited systemic reaction was 62.9% in Group 1 and 63.5% in Group 2.

Unsolicited AEs

The proportion of subjects who experienced at least 1 unsolicited AE was 22.5% in Group 1 and 25.2% in Group 2. There were 1.2% of subjects in Group 1 and 1.8% of subjects in Group 2 with at least 1 unsolicited AR. After the 2nd dose of MenACYW conjugate vaccine or MENVEO, the proportion of subjects with at least 1 unsolicited non-serious injection site AR was 1.2% in Group 1 and 1.3% in Group 2.

Discontinuation due to AEs

Within 30 days of the 4-month vaccinations, 1 subject (0.1%) in Group 2 was discontinued from the study due to 1 AE (congenital absence of bile ducts). No discontinuation due to AE was reported in Group 1.

Serious AEs including AESIs and MAAEs

Within 30 days of the 4-month vaccinations, there were 7 subjects (0.4%) in Group 1 and 1 subject (0.1%) in Group 2 with at least 1 SAE, 1 (0.1%) subject in Group 1 and no subject in Group 2 with at least 1 AESI, and 252 subjects (15.6%) in Group 1 and 151 subjects (18.3%) in Group 2 with at least 1 MAAE.

During the study including the 6-month follow-up period, there were 15 subjects (0.9%) in Group 1 and 7 subjects (0.8%) in Group 2 with at least 1 SAE, 1 subject (0.1%) in Group 1 and 1 subject (0.1%) in Group 2 with at least 1 AESI, and 472 subjects (29.1%) in Group 1 and 265 subjects (32.0%) in Group 2 with at least 1 MAAE.

Subjects aged 6 months (SafAS3) - 3rd dose of MenACYW conjugate vaccine or MENVEO

No immediate unsolicited AEs were reported within 30 minutes of the 6-month vaccinations in any group.

Solicited reactions

The proportion of subjects with at least 1 solicited injection site reaction was 55.3% in Group 1 and 53.8% in Group 2. After the 3rd dose of MenACYW conjugate vaccine or MENVEO, there were 48.0% of subjects in Group 1 and 46.3% of subjects in Group 2. The proportion of subjects with at least 1 solicited systemic reaction was 57.9% in both groups.

Unsolicited AEs

The proportion of subjects with at least 1 unsolicited AE was 29.4% in Group 1 and 27.8% in Group 2. There were 2.1% of subjects in Group 1 and 1.5% of subjects in Group 2 with at least 1 unsolicited AR. After the 3rd dose of MenACYW conjugate vaccine or MENVEO, the proportion of subjects with at least 1 unsolicited non-serious injection site AR was 1.9% in Group 1 and 1.5% in Group 2.

Discontinuation due to AEs

No discontinuation from the study due to AEs occurred within 30 days of the 6-month vaccinations in any group.

Serious AEs including AESIs and MAAEs

Within 30 days of the 6-month vaccinations, there were 17 subjects (1.1%) in Group 1 and 3 subjects (0.4%) in Group 2 with at least 1 SAE. No AESIs were reported in any group. A total of 306 subjects (19.8%) in Group 1 and 153 subjects (19.3%) in Group 2 experienced at least 1 MAAE.

During the study including the 6-month follow-up period, there were 41 subjects (2.7%) in Group 1 and 13 subjects (1.6%) in Group 2 with at least 1 SAE, 4 subjects (0.3%) in Group 1 and 1 subject (0.1%) in Group 2 with at least 1 AESI, and 754 subjects (48.9%) in Group 1 and 365 subjects (46.0%) in Group 2 with at least 1 MAAE.

Subjects aged 12 months (SafAS4) - 4th dose of MenACYW conjugate vaccine (Group 1a) or MENVEO (Groups 2a and 2b)

No immediate unsolicited AEs were reported within 30 minutes of the 12-month vaccinations in any group.

Solicited reactions

The proportion of subjects with at least 1 solicited injection site reaction was 52.4% in Group 1a, 53.4% in Group 1b, 56.4% in Group 2a, and 53.8% in Group 2b. After the 4th dose of MenACYW conjugate vaccine or MENVEO, there were 42.5% of subjects in Group 1a, 45.4% of subjects in Group 2a, and 44.0% in Group 2b. The proportion of subjects with at least 1 solicited systemic reaction was 55.2% in Group 1a, 53.6% in Group 1b, 58.5% in Group 2a, and 50.7% in Group 2b.

Unsolicited AEs

The proportion of subjects with at least 1 unsolicited AE was 28.8% in Group 1a, 20.1% in Group 1b, 25.8% in Group 2a, and 22.8% in Group 2b. There were 2.3% of subjects in Group 1a, 2.3% of subjects in Group 2a, and 1.3% of subjects in Group 2b with at least 1 unsolicited AR.

After the 4th dose of MenACYW conjugate vaccine or MENVEO, the proportion of subjects who experienced at least 1 unsolicited non-serious injection site AR was 2.1% in Group 1a, 2.3% in Group 2a, and 0.4% in Group 2b.

Discontinuation due to AEs

There were no AEs that caused subjects to discontinue from the study within 30 days of the 12-month vaccinations in any group.

Serious AEs including AESIs and MAAEs

Within 30 days of the 12-month vaccinations, there were 4 subjects (0.4%) in Group 1a and 1 subject (0.2%) in Group 1b and no subject in Groups 2a and 2b with at least 1 SAE, 1 subject (0.1%) in Group 1a and no subject in Groups 1b, 2a, and 3b with at least 1 AESI, and 156 subjects (16.6%) in Group 1a, 62 subjects (13.1%) in Group 1b, 72 subjects (15.0%) in Group 2a, and 36 subjects (15.8%) subjects in Group 2b with at least 1 MAAE.

During the study including the 6-month follow-up period, there were 14 subjects (1.5%) in Group 1a, 6 subjects (1.3%) in Group 1b, 5 subjects (1.0%) in Group 2a, and 1 subject (0.4%) in Group 2b with at least 1 SAE. There were 3 subjects (0.3%) in Group 1a, 2 subjects (0.4%) in Group 1b, 2 subjects (0.4%) in Group 2a, and no subject in Group 2b with at least 1 AESI. A total of 335 subjects (35.7%) in Group 1a, 159 subjects (33.7%) in Group 1b, 159 subjects (33.1%) in Group 2a, and 70 subjects (30.7%) in Group 2b experienced at least 1 MAAE.

Subjects aged 15 months (SafAS5) - 4th dose of MenACYW conjugate vaccine (Group 1b)

There was 1 subject (0.2%; rash) in Group 2a who reported at least 1 immediate unsolicited AE within 30 minutes of the 15-month vaccinations which was assessed as unrelated to study vaccine by the Investigator. No immediate unsolicited AE was reported in Groups 1b and 2b.

Solicited reactions

The proportion of subjects with at least 1 solicited injection site reaction was 52.1% in Group 1b, 46.5% in Group 2a, and 44.7% in Group 2b. After the 4th dose of MenACYW conjugate vaccine, there were 46.1% of subjects in Group 1b. The proportion of subjects with at least 1 solicited systemic reaction was 50.1% in Group 1b, 47.0% in Group 2a, and 46.2% in Group 2b.

Unsolicited AEs

The proportion of subjects who experienced at least 1 unsolicited AE was 21.6% in Group 1b, 18.6% in Group 2a, and 21.9% in Group 2b. The proportion of subjects with at least 1 unsolicited AR was 1.8% in Group 1b. After the 4th dose of MenACYW conjugate vaccine, they were 1.4% in Group 1b with at least 1 unsolicited non-serious injection site AR.

Discontinuation due to AEs

There were no AEs that caused subjects to discontinue from the study within 30 days of the 15-month vaccinations in any group.

Serious AEs including AESIs and MAAEs

Within 30 days of the 15-month vaccinations, there were 2 subjects (0.5%) in Group 1b, 1 subject (0.2%) in Group 2a, and 1 subject (0.5%) in Group 2b who reported at least 1 SAE.

There was 1 subject (0.2%) subject in Group 1b and no subject in Groups 2a and 2b with at least 1 AESI. A total of 59 subjects (13.3%) in Group 1b, 53 subjects (12.5%) in Group 2a, and 34 subjects (15.5%) in Group 2b experienced at least 1 MAAE.

During the study including the 6-month follow-up period, there were 6 subjects (1.4%) in Group 1b, 3 subjects (0.7%) in Group 2a, and 1 subject (0.5%) in Group 2b with at least 1 SAE.

There were 2 subjects (0.5%) in Group 1b, 1 subject (0.2%) in Group 2a, and no subject in Group 2b with at least 1 AESI. A total of 133 subjects (30.0%) in Group 1b, 140 subjects (32.9%) in Group 2a, and 68 subjects (31.1%) in Group 2b experienced at least 1 MAAE.

Safety Analysis Set for All 4-dose vaccination (SafAS6)

In the SafAS6, there were 1 subject (<0.1%; infantile spitting up) in Group 1 and 1 subject (0.1%; rash) in Group 2 with at least 1 immediate unsolicited AE within 30 minutes of any vaccination. None were assessed as related to study vaccine by the Investigator in any group.

Solicited reactions

The proportion of subjects who experienced at least 1 solicited injection site reaction after any vaccination was 90.0% in Group 1 and 90.2% in Group 2. After any vaccination with MenACYW conjugate vaccine or MENVEO, there were 75.3% of subjects in Group 1 and 73.4% of subjects in Group 2. The proportion of subjects with at least 1 solicited systemic reaction was 84.3% in Group 1 and 84.9% in Group 2.

Unsolicited AEs

The proportion of subjects with at least 1 unsolicited AE after any vaccination was 59.6% in Group 1 and 58.9% in Group 2. There were 6.1% of subjects in Group 1 and 7.4% of subjects in Group 2 with at least 1 unsolicited AR. After any vaccination of MenACYW conjugate vaccine or MENVEO, the proportion of subjects who experienced at least 1 unsolicited non-serious injection site AR was 5.6% in Group 1 and 6.5% in Group 2.

Serious AEs including AESIs and MAAEs

Within 30 days of any vaccination, there were 33 subjects (2.4%) in Group 1 and 8 subjects (1.1%) in Group 2 with at least 1 SAE, 3 subjects (0.2%) in Group 1 and no subject in Group 2 with at least 1 AESI, and 606 subjects (44.1%) in Group 1 and 326 subjects (46.2%) in Group 2 with at least 1 MAAE.

During the study including the 6-month follow-up period, there were 79 subjects (5.7%) in Group 1 and 30 subjects (4.3%) in Group 2 with at least 1 SAE, 12 subjects (0.9%) in Group 1 and 4 subjects (0.6%) in Group 2 with at least 1 AESI, and 918 subjects (66.8%) in Group 1 and 464 subjects (65.8%) in Group 2 with at least 1 MAAE.

During the study including the 6-month follow-up period, 1 death was reported. One subject (0.1%) in Group 1 died of a cardiac arrest, 6 days after receiving the 1st dose of MenACYW conjugate vaccine. This event was assessed as unrelated to study vaccine.

Other results:

- The impact of the coronavirus disease 2019 (COVID-19) pandemic situation was assessed as negligeable.
- Subgroup analyses per gender and race did not reveal any difference.

- Subgroup analyses per birth status at baseline did not show any differences of immunogenicity and safety results between preterm and full-term subjects (details are provided below).

Subgroup Analysis by Preterm and Full-term Birth Status - Immunogenicity

Additional descriptive immunogenicity data and analyses per birth status at baseline following the administration of MenACYW conjugate vaccine are presented in this section. The analyses are based on the following numbers of subjects in Group 1:

- 66 preterm subjects and 861 full-term subjects in the PPAS1
- 71 preterm subjects and 871 full-term subjects in the PPAS2
- 61 preterm subjects and 922 full-term subjects in the PPAS3

Overall, the immunogenicity results between preterm and full-term subjects in Group 1 were comparable.

hSBA Titers After a 3-Dose Series by Preterm and Full-term Birth Status

hSBA GMTs before the 1st dose and after the 3rd dose

In Group 1, the hSBA GMTs from D0 before the 1st dose to D30 after the 3rd dose at the 6-month vaccinations in the PPAS1 were comparable between preterm and full-term subjects for all serogroups:

• For serogroup A

- At D0 before the 1st dose: 3.31 in preterm subjects and 3.37 in full-term subjects
- At D30 after the 3rd dose: 17.7 in preterm subjects and 26.0 in full-term subjects

• For serogroup C

- At D0 before the 1st dose: 2.54 in preterm subjects and 2.77 in full-term subjects
- At D30 after the 3rd dose: 411 in preterm subjects and 389 in full-term subjects

• For serogroup Y

- At D0 before the 1st dose: 2.81 in preterm subjects and 2.95 in full-term subjects
- At D30 after the 3rd dose: 92.6 in preterm subjects and 87.8 in full-term subjects

• For serogroup W

- At D0 before the 1st dose: 2.95 in preterm subjects and 2.86 in full-term subjects
- At D30 after the 3rd dose: 80.6 in preterm subjects and 99.5 in full-term subjects

Distribution of hSBA titers after the 3rd dose

The distribution of hSBA titers at D30 after the 3rd dose at the 6-month vaccinations in the PPAS1 was comparable between preterm and full-term subjects in Group 1. The percentages of subjects with hSBA titer $\geq$ 1:4 to $\geq$ 1:256 ranged:

- From 85.5% to 5.5% in preterm subjects and from 87.9% to 12.9% in full-term subjects for serogroup A
- from 100% to 86.0% in preterm subjects and from 99.2% to 77.3% in full-term subjects for serogroup C

- From 100% to 25.0% in preterm subjects and from 99.0% to 29.1% in full-term subjects for serogroup Y
- From 98.4% to 25.4% in preterm subjects and from 99.6% to 29.3% in full-term subjects for serogroup W

hSBA antibody titer ≥ 1:4 and ≥ 1:8 after the 3rd dose

The number and percentage of subjects with hSBA titer ≥ 1:4 and ≥ 1:8 at D30 after the 3rd dose at the 6-month vaccinations in the PPAS1 were comparable between preterm and full-term subjects in Group 1 (Table 27).

• The percentage of subjects with hSBA titers ≥ 1:4 ranged from 85.5% (for serogroup A) to 100% (for serogroups C and Y) for preterm subjects and from 87.9% (for serogroup A) to 99.6% (for serogroup W) for full-term subjects.

• The percentage of subjects with hSBA titers ≥ 1:8 ranged from 76.4% (for serogroup A) to 100% (for serogroup C) for preterm subjects and from 78.0% (for serogroup A) to 99.0% (for serogroup C) for full-term subjects.

Table 22: Number and percentage of subjects with hSBA titer >=1:4 and >=1:8 by preterm and full term at D30 after the 6-month vaccinations – Per-Protocol Analysis Set 1

		Preterm Group 1 (N=66)			Full-term Group 1 (N=861)		
Serogroup	hSBA Titers	n/M	%	95% CI	n/M	%	95% CI
A	>=1:4	47/55	85.5	(73.3 ; 93.5)	700/796	87.9	(85.5 ; 90.1)
	>=1:8	42/55	76.4	(63.0 ; 86.8)	621/796	78.0	(75.0 ; 80.8)
C	>=1:4	57/57	100	(93.7 ; 100)	771/777	99.2	(98.3 ; 99.7)
	>=1:8	57/57	100	(93.7 ; 100)	769/777	99.0	(98.0 ; 99.6)
Y	>=1:4	60/60	100	(94.0 ; 100)	792/800	99.0	(98.0 ; 99.6)
	>=1:8	59/60	98.3	(91.1 ; 100)	786/800	98.3	(97.1 ; 99.0)
W	>=1:4	62/63	98.4	(91.5 ; 100)	816/819	99.6	(98.9 ; 99.9)
	>=1:8	61/63	96.8	(89.0 ; 99.6)	809/819	98.8	(97.8 ; 99.4)

N: number of subjects in per-protocol analysis set 1, for infant vaccinations
M: number of subjects with valid serology results for the particular serogroup and hSBA titers
n: number of subjects experiencing the endpoint listed in the first 2 columns
Percentages are based on M.
Group 1 MenACYW conjugate vaccine and routine pediatric vaccines
Preterm infant born at gestational age <37 weeks ; full-term infant born at gestational age >=37 weeks
For one subject, gestational age was not collected.

hSBA antibody titer ≥ 4-fold rise from pre-1st dose to post-3rd dose

The number and percentage of subjects with ≥ 4-fold rise of hSBA titer from pre-1st dose to post-3rd dose at 6 months of age in the PPAS1 were comparable between preterm and full-term subjects in Group 1 for all serogroups.

The percentages of subjects with ≥ 4-fold rise of hSBA titer were:

- For serogroup A: 68.1% in preterm subjects and 64.1% in full-term subjects
- For serogroup C: 100% in preterm subjects and 96.1% in full-term subjects
- For serogroup Y: 97.9% in preterm subjects and 88.1% in full-term subjects
- For serogroup W: 91.1% in preterm subjects and 93.0% in full-term subjects

hSBA seroresponse from pre-1st dose to post-3rd dose

The hSBA seroresponse rates are the percentages of subjects with 4-fold rise of hSBA titers at D30 after the 3rd dose at the 6-month vaccinations by preterm and full-term birth status (Table 23).

Table 23: Summary of hSBA vaccine seroresonse rate by preterm and full-term at D30 after the 3rd-dose vaccinations – pre-protocol analysis set 1

	Preterm Group 1 (N=66)			Full-term Group 1 (N=861)		
Serogroup	n/M	%	95% CI	n/M	%	95% CI
A	32/47	68.1	(52.9 ; 80.9)	407/635	64.1	(60.2 ; 67.8)
C	50/50	100	(92.9 ; 100)	616/641	96.1	(94.3 ; 97.5)
Y	46/47	97.9	(88.7 ; 99.9)	576/654	88.1	(85.3 ; 90.5)
W	51/56	91.1	(80.4 ; 97.0)	635/683	93.0	(90.8 ; 94.8)

N: number of subjects in per-protocol analysis set 1, for infant vaccinations; M: number of subjects with valid serology results for the particular serogroup and time point
n: number of subjects experiencing the endpoint listed in the first column and met the criterion
hSBA vaccine seroresponse for serogroups A, C, Y and W is defined as: for a subject with a pre-1st dose vaccinations titer < 1:8, the post-3rd dose vaccinations titer must be >= 1:16; for a subject with a pre-1st dose vaccinations titer >= 1:8, the post-3rd dose vaccinations titer must be at least 4-fold greater than the pre-1st dose vaccinations titer.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines
Preterm infant born at gestational age <37 weeks ; full-term infant born at gestational age >=37 weeks; For one subject, gestational age was not collected.

hSBA Titers before the Administration of the 4th Dose at 12 Months of Age (Immune Persistence) by Preterm and Full-Term Birth Status

hSBA GMTs after the 3rd dose and before the 4th dose

In Group 1a, the GMTs hSBA at D30 after the 3rd dose and D0 before the 4th dose at the 12-month vaccinations in the PPAS2 were comparable between preterm and full-term subjects for all serogroups, except for serogroup A at D30 after the 3rd dose for which the GMTs hSBA were lower in preterm than in full-term subjects in Group 1a. Results were comparable between preterm and full-term subjects of the Group 1b:

- For serogroup A
  - At D30 after the 3rd dose:
    - in Group 1a: 12.6 in preterm subjects and 26.0 in full-term subjects
    - in Group 1b: 23.0 in preterm subjects and 23.3 in full-term subjects
  - At D0 before the 4th dose:
    - in Group 1a: 8.83 in preterm subjects and 9.37 in full-term subjects
    - in Group 1b: 8.00 in preterm subjects and 7.89 in full-term subjects
- For serogroup C
  - At D30 after the 3rd dose:
    - in Group 1a: 387 in preterm subjects and 364 in full-term subjects
    - in Group 1b: 340 in preterm subjects and 392 in full-term subjects
  - At D0 before the 4th dose:
    - in Group 1a: 52.4 in preterm subjects and 58.2 in full-term subjects
    - in Group 1b: 28.0 in preterm subjects and 37.8 in full-term subjects
- For serogroup Y
  - At D30 after the 3rd dose:
    - in Group 1a: 93.0 in preterm subjects and 82.3 in full-term subjects
    - in Group 1b: 83.3 in preterm subjects and 83.3 in full-term subjects

- At D0 before the 4th dose:
- in Group 1a: 41.7 in preterm subjects and 43.0 in full-term subjects
- in Group 1b: 36.6 in preterm subjects and 44.4 in full-term subjects

• For serogroup W

- At D30 after the 3rd dose:
- in Group 1a: 83.6 in preterm subjects and 93.5 in full-term subjects
- in Group 1b: 65.9 in preterm subjects and 101 in full-term subjects
- At D0 before the 4th dose:
- in Group 1a: 55.7 in preterm subjects and 57.9 in full-term subjects
- in Group 1b: 44.1 in preterm subjects and 56.8 in full-term subjects

hSBA antibody titer ≥ 1:4 and ≥ 1:8 after the 3rd dose and before the 4th dose

In the PPAS2, the number and percentage of subjects with hSBA titer ≥ 1:4 and ≥ 1:8 at D30 after the 3rd dose at 6 months of age and at D0 before the 4th dose at the 12-month vaccinations (Group 1a) and at the 15-month vaccinations (Group 1b) were comparable between preterm and full-term subjects (Table 29).

At D30 after the 3rd dose, the percentage of subjects with:

• hSBA titers ≥ 1:4 ranged

- From 80.0% (serogroup A in Group 1a) to 100% (serogroups C, Y and W in Group 1a) for preterm subjects and
- From 87.5% (serogroup A in Group 1a) to 99.8% (serogroup W in Group 1a) for full-term subjects

• hSBA titers ≥ 1:8 ranged

- From 65.7% (serogroup A in Group 1a) to 100% (serogroup C in both groups and serogroups Y and W in Group 1a) for preterm subjects and
- From 76.3% (serogroup A in Group 1b) to 99.0% (serogroup C in Group 1a) for full-term subjects

At D0 before the 4th dose, the percentage of subjects with

• hSBA titers ≥ 1:4 ranged

- From 79.2% (serogroup A in Group 1b) to 100% (serogroups Y and W in Group 1a) for preterm subjects and
- From 82.6% (serogroup A in Group 1a) to 99.6% (serogroup W in Group 1b) for full-term subjects

• hSBA titers ≥ 1:8 ranged

- From 57.1% (serogroup A in Group 1a) to 97.8% (serogroup W for Group 1a) for preterm subjects and
- From 55.6% (serogroup A in Group 1b) to 97.2% (serogroup W in Group 1a) for full-term subjects

Table 24: Number and percentage of subjects with hSBA titer >=1:4 and >=1:8 by preterm and full-term for groups 1a and 1b – Per-Protocol Analysis Set 2

			Preterm						Full-term					
			Group 1a (N=45)			Group 1b (N=26)			Group 1a (N=602)			Group 1b (N=269)		
Serogroup	Time Point	hSBA Titers	n/M	%	95% CI	n/M	%	95% CI	n/M	%	95% CI	n/M	%	95% CI
A	D30 after 3rd dose	>=1:4	28/35	80.0	(63.1 ; 91.6)	20/21	95.2	(76.2 ; 99.9)	448/512	87.5	(84.3 ; 90.2)	210/236	89.0	(84.3 ; 92.7)
		>=1:8	23/35	65.7	(47.8 ; 80.9)	18/21	85.7	(63.7 ; 97.0)	400/512	78.1	(74.3 ; 81.6)	180/236	76.3	(70.3 ; 81.5)
	D0 before 4th dose	>=1:4	34/42	81.0	(65.9 ; 91.4)	19/24	79.2	(57.8 ; 92.9)	483/585	82.6	(79.2 ; 85.6)	215/259	83.0	(77.9 ; 87.4)
		>=1:8	24/42	57.1	(41.0 ; 72.3)	15/24	62.5	(40.6 ; 81.2)	346/585	59.1	(55.0 ; 63.2)	144/259	55.6	(49.3 ; 61.7)
C	D30 after 3rd dose	>=1:4	37/37	100	(90.5 ; 100)	22/22	100	(84.6 ; 100)	501/505	99.2	(98.0 ; 99.8)	228/231	98.7	(96.3 ; 99.7)
		>=1:8	37/37	100	(90.5 ; 100)	22/22	100	(84.6 ; 100)	500/505	99.0	(97.7 ; 99.7)	228/231	98.7	(96.3 ; 99.7)
	D0 before 4th dose	>=1:4	42/45	93.3	(81.7 ; 98.6)	21/26	80.8	(60.6 ; 93.4)	566/592	95.6	(93.6 ; 97.1)	240/268	89.6	(85.3 ; 92.9)
		>=1:8	41/45	91.1	(78.8 ; 97.5)	19/26	73.1	(52.2 ; 88.4)	551/592	93.1	(90.7 ; 95.0)	227/268	84.7	(79.8 ; 88.8)
Y	D30 after 3rd dose	>=1:4	39/39	100	(91.0 ; 100)	21/21	100	(83.9 ; 100)	514/519	99.0	(97.8 ; 99.7)	237/239	99.2	(97.0 ; 99.9)
		>=1:8	39/39	100	(91.0 ; 100)	20/21	95.2	(76.2 ; 99.9)	511/519	98.5	(97.0 ; 99.3)	236/239	98.7	(96.4 ; 99.7)
	D0 before 4th dose	>=1:4	42/42	100	(91.6 ; 100)	24/26	92.3	(74.9 ; 99.1)	586/591	99.2	(98.0 ; 99.7)	264/269	98.1	(95.7 ; 99.4)
		>=1:8	41/42	97.6	(87.4 ; 99.9)	24/26	92.3	(74.9 ; 99.1)	572/591	96.8	(95.0 ; 98.1)	258/269	95.9	(92.8 ; 97.9)
W	D30 after 3rd dose	>=1:4	39/39	100	(91.0 ; 100)	23/24	95.8	(78.9 ; 99.9)	531/532	99.8	(99.0 ; 100)	243/245	99.2	(97.1 ; 99.9)
		>=1:8	39/39	100	(91.0 ; 100)	22/24	91.7	(73.0 ; 99.0)	525/532	98.7	(97.3 ; 99.5)	241/245	98.4	(95.9 ; 99.6)
	D0 before 4th dose	>=1:4	45/45	100	(92.1 ; 100)	24/26	92.3	(74.9 ; 99.1)	592/599	98.8	(97.6 ; 99.5)	268/269	99.6	(97.9 ; 100)
		>=1:8	44/45	97.8	(88.2 ; 99.9)	23/26	88.5	(69.8 ; 97.6)	582/599	97.2	(95.5 ; 98.3)	258/269	95.9	(92.8 ; 97.9)

N : number of subjects in per-protocol analysis set 2
M: number of subjects with valid serology results for the particular serogroup and time point
n: number of subjects experiencing the endpoint listed in the first 3 columns
Percentages are based on M.
Group 1a: MenACYW conjugate vaccine and routine vaccines at 2, 4, 6, and 12 to 15 months of age
Group 1b: MenACYW conjugate vaccine at 2, 4, 6, and 15 to18 months of age and routine vaccines at 2, 4, 6, 12 to 15 months of age
Preterm infant born at gestational age <37 weeks ; full-term infant born at gestational age >=37 weeks
For one subject, gestational age was not collected.

hSBA Titers After a 4-Dose Series by Preterm and Full-term Birth Status

hSBA GMTs before the 1st dose and after the 4th dose

In the PPAS3, the hSBA GMTs at D0 before the 1st dose to D30 after the 4th dose at the 12-month vaccinations (Group 1a) and at the 15-month vaccinations (Group 1b) were comparable between preterm and full-term subjects for all serogroups (Appendix 15, Table 59):

• For serogroup A

o At D0 before the 1st dose:

in Group 1a: 3.91 in preterm subjects and 3.39 in full-term subjects

in Group 1b: 2.61 in preterm subjects and 3.27 in full-term subjects

o At D30 after the 4th dose:

in Group 1a: 40.3 in preterm subjects and 69.2 in full-term subjects

in Group 1b: 33.2 in preterm subjects and 83.0 in full-term subjects

• For serogroup C

o At D0 before the 1st dose:

in Group 1a: 2.86 in preterm subjects and 2.83 in full-term subjects

in Group 1b: 2.41 in preterm subjects and 2.88 in full-term subjects

o At D30 after the 4th dose:

in Group 1a: 436 in preterm subjects and 697 in full-term subjects

in Group 1b: 512 in preterm subjects and 664 in full-term subjects

• For serogroup Y

o At D0 before the 1st dose:

in Group 1a: 3.24 in preterm subjects and 3.03 in full-term subjects

in Group 1b: 2.69 in preterm subjects and 3.01 in full-term subjects

o At D30 after the 4th dose:

in Group 1a: 285 in preterm subjects and 297 in full-term subjects

in Group 1b: 287 in preterm subjects and 375 in full-term subjects

• For serogroup W

o At D0 before the 1st dose:

in Group 1a: 3.46 in preterm subjects and 2.84 in full-term subjects

in Group 1b: 2.89 in preterm subjects and 2.88 in full-term subjects

o At D30 after the 4th dose:

in Group 1a: 365 in preterm subjects and 389 in full-term subjects

in Group 1b: 724 in preterm subjects and 830 in full-term subjects

Distribution of hSBA titers after the 4th dose

In the PPAS3, the distribution of hSBA titers at D30 after the 4th dose at the 12-month vaccinations (Group 1a) and at the 15-month vaccinations (Group 1b) was comparable between preterm and full-term subjects. The percentages of subjects with hSBA titer ≥ 1:4 to ≥ 1:256 ranged:

• For serogroup A

o In Group 1a: from 91.7% to 16.7% in preterm subjects and from 91.4% to 34.7% in full-term subjects

o In Group 1b: from 89.5% to 15.8% in preterm subjects and from 97.3% to 34.5% in full-term subjects

• For serogroup C

o In Group 1a: from 100% to 79.5% in preterm subjects and from 99.5% to 86.4% in full-term subjects

o In Group 1b: from 100% to 82.4% in preterm subjects and from 99.6% to 84.4% in full-term subjects

• For serogroup Y

o In Group 1a: from 100% to 64.1% in preterm subjects and from 99.5% to 68.8% in full-term subjects

o In Group 1b: from 100% to 66.7% in preterm subjects and from 99.3% to 75.1% in full-term subjects

• For serogroup W

o In Group 1a: from 100% to 70.3% in preterm subjects and from 99.5% to 75.9% in full-term subjects

o In Group 1b: from 100% to 77.8% in preterm subjects and from 100% to 87.1% in full-term subjects

hSBA antibody titer ≥ 1:4 and ≥ 1:8 after the 4th dose

In the PPAS3, the number and percentage of subjects with hSBA titer ≥ 1:4 and ≥ 1:8 at D30 after the 4th dose at the 12-month vaccinations (Group 1a) and at the 15-month vaccinations (Group 1b) were comparable between preterm and full-term subjects (Table 30).

At D30 after the 4th dose, the percentage of subjects with:

• hSBA titers ≥ 1:4 ranged

o From 89.5% (for serogroup A in Group 1b) to 100% (for serogroups C, Y and W in both groups) for preterm subjects and

o From 91.4% (for serogroup A in Group 1a) to 100% (for serogroup W in Group 1b) for full-term subjects

• hSBA titers ≥ 1:8 ranged

o From 84.2% (for serogroup A in Group 1b) to 100% (for serogroups C, Y and W in both groups) for preterm subjects and

o From 87.6% (for serogroup A in Group 1a) to 100% (for serogroup W in Group 1b) for full-term subjects

hSBA antibody titer ≥ 4-fold rise from pre-1st dose to post-4th dose

In the PPAS3, the number and percentage of subjects with ≥ 4-fold rise of hSBA titers from pre-1st dose to post-4th dose at the 12-month vaccinations (Group 1a) and at the 15-month vaccinations (Group 1b) in the PPAS3 were comparable between preterm and full-term subjects for all serogroups:

• For serogroup A:

o In Group 1a: 77.8% in preterm subjects and 79.5% in full-term subjects

o In Group 1b: 84.6% in preterm subjects and 84.3% in full-term subjects

• For serogroup C:

o In Group 1a: 97.1% in preterm subjects and 97.0% in full-term subjects

o In Group 1b: 100% in preterm subjects and 97.8% in full-term subjects

• For serogroup Y:

o In Group 1a: 100% in preterm subjects and 96.1% in full-term subjects

o In Group 1b: 100% in preterm subjects and 98.2% in full-term subjects

• For serogroup W:

o In Group 1a: 100% in preterm subjects and 97.4% in full-term subjects

o In Group 1b: 100% in preterm subjects and 98.7% in full-term subjects

hSBA seroresponse from pre-1st dose to post-4th dose

The percentages of subjects with 4-fold rise of hSBA titer are the hSBA vaccine seroresponse rates from pre-1st dose to post-4th dose at the 12-month vaccinations (Group 1) and at the 15-month vaccinations (Group 1b) in the PPAS3 (Table 26)

Table 25: Number and percentage of subjects with hSBA titer >=1:4 and >=1:8 by preterm and full-term at D30 after 4th-dose vaccinations for groups 1a and 1b – Per-Protocol Analysis set 3

		Preterm						Full-term					
		Group 1a (N=41)			Group 1b (N=20)			Group 1a (N=634)			Group 1b (N=288)		
Serogroup	hSBA Titers	n/M	%	95% CI	n/M	%	95% CI	n/M	%	95% CI	n/M	%	95% CI
A	>=1:4	33/36	91.7	(77.5 ; 98.2)	17/19	89.5	(66.9 ; 98.7)	554/606	91.4	(88.9 ; 93.5)	257/264	97.3	(94.6 ; 98.9)
	>=1:8	32/36	88.9	(73.9 ; 96.9)	16/19	84.2	(60.4 ; 96.6)	531/606	87.6	(84.7 ; 90.1)	246/264	93.2	(89.4 ; 95.9)
C	>=1:4	39/39	100	(91.0 ; 100)	17/17	100	(80.5 ; 100)	613/616	99.5	(98.6 ; 99.9)	274/275	99.6	(98.0 ; 100)
	>=1:8	39/39	100	(91.0 ; 100)	17/17	100	(80.5 ; 100)	612/616	99.4	(98.3 ; 99.8)	273/275	99.3	(97.4 ; 99.9)
Y	>=1:4	39/39	100	(91.0 ; 100)	18/18	100	(81.5 ; 100)	609/612	99.5	(98.6 ; 99.9)	275/277	99.3	(97.4 ; 99.9)
	>=1:8	39/39	100	(91.0 ; 100)	18/18	100	(81.5 ; 100)	606/612	99.0	(97.9 ; 99.6)	275/277	99.3	(97.4 ; 99.9)
W	>=1:4	37/37	100	(90.5 ; 100)	18/18	100	(81.5 ; 100)	611/614	99.5	(98.6 ; 99.9)	271/271	100	(98.6 ; 100)
	>=1:8	37/37	100	(90.5 ; 100)	18/18	100	(81.5 ; 100)	610/614	99.3	(98.3 ; 99.8)	271/271	100	(98.6 ; 100)

N: number of subjects in per-protocol analysis set 3
M: number of subjects with valid serology results for the particular serogroup
n: number of subjects experiencing the endpoint listed in the first 2 columns
Percentages are based on M.
Group 1a: MenACYW conjugate vaccine and routine vaccines at 2, 4, 6, and 12 to 15 months of age
Group 1b: MenACYW conjugate vaccine at 2, 4, 6, and 15 to18 months of age and routine vaccines at 2, 4, 6, 12 to 15 months of age
Preterm infant born at gestational age <37 weeks ; full-term infant born at gestational age >=37 weeks
For one subject, gestational age was not collected.

Table 26: Summary of hSBA vaccine seroresonse rate by preterm and full-term from D0 pre-1st dose to D30 afterh the 4th dose vaccination for groups 1a and 1b – Per-Protocol analysis Set 3

	Preterm						Full-term					
	Group 1a (N=41)			Group 1b (N=20)			Group 1a (N=634)			Group 1b (N=288)		
Serogroup	n/M	%	95% CI	n/M	%	95% CI	n/M	%	95% CI	n/M	%	95% CI
A	21/27	77.8	(57.7 ; 91.4)	11/13	84.6	(54.6 ; 98.1)	377/474	79.5	(75.6 ; 83.1)	177/210	84.3	(78.6 ; 88.9)
C	33/34	97.1	(84.7 ; 99.9)	14/14	100	(76.8 ; 100)	481/496	97.0	(95.1 ; 98.3)	221/226	97.8	(94.9 ; 99.3)
Y	33/33	100	(89.4 ; 100)	14/14	100	(76.8 ; 100)	471/490	96.1	(94.0 ; 97.6)	219/223	98.2	(95.5 ; 99.5)
W	35/35	100	(90.0 ; 100)	14/14	100	(76.8 ; 100)	492/505	97.4	(95.6 ; 98.6)	225/228	98.7	(96.2 ; 99.7)

N: number of subjects in per-protocol analysis set 3; M: number of subjects with valid serology results for the particular serogroup
n: number of subjects experiencing the endpoint listed in the first column and met the criterion; Percentages are based on M
hSBA vaccine seroresponse: for a subject with a pre-1st dose vaccinations titer < 1:8, the post-4th dose vaccinations titer must be >= 1:16;
For a subject with a pre-1st dose vaccinations titer >= 1:8, the post-4th vaccinations titer must be at least 4-fold greater than the pre-1st dose vaccinations titer.
Group 1a: MenACYW conjugate vaccine and routine vaccines at 2, 4, 6, and 12 to 15 months of age
Group 1b: MenACYW conjugate vaccine at 2, 4, 6, and 15 to18 months of age and routine vaccines at 2, 4, 6, 12 to 15 months of age
Preterm infant born at gestational age <37 weeks ; full-term infant born at gestational age >=37 weeks
For one subject, gestational age was not collected.

hSBA Titers From Pre- to Post-4th Dose by Preterm and Full-term Birth Status

hSBA GMTs before and after the 4th dose

In the PPAS3, the hSBA GMTs at D0 before the 4th dose and at D30 after the 4th dose at the 12-month vaccinations (Group 1a) and at the 15-month vaccinations (Group 1b) were comparable between preterm and full-term subjects for all serogroups (Table 27):

• For serogroup A

o At D0 before the 4th dose:

In Group 1a: 9.43 in preterm subjects and 10.7 in full-term subjects

In Group 1b: 6.60 in preterm subjects and 8.13 in full-term subjects

o At D30 after the 4th dose:

In Group 1a: 40.3 in preterm subjects and 69.2 in full-term subjects

In Group 1b: 33.2 in preterm subjects and 83.0 in full-term subjects

• For serogroup C

o At D0 before the 4th dose:

In Group 1a: 52.9 in preterm subjects and 61.9 in full-term subjects

In Group 1b: 40.8 in preterm subjects and 41.4 in full-term subjects

o At D30 after the 4th dose:

In Group 1a: 436 in preterm subjects and 697 in full-term subjects

In Group 1b: 512 in preterm subjects and 664 in full-term subjects

• For serogroup Y

o At D0 before the 4th dose:

In Group 1a: 43.6 in preterm subjects and 43.5 in full-term subjects

In Group 1b: 32.0 in preterm subjects and 43.3 in full-term subjects

o At D30 after the 4th dose:

In Group 1a: 285 in preterm subjects and 297 in full-term subjects

In Group 1b: 287 in preterm subjects and 375 in full-term subjects

• For serogroup W

o At D0 before the 4th dose:

In Group 1a: 52.9 in preterm subjects and 58.3 in full-term subjects

In Group 1b: 42.8 in preterm subjects and 59.0 in full-term subjects

o At D30 after the 4th dose:

In Group 1a: 365 in preterm subjects and 389 in full-term subjects

In Group 1b: 724 in preterm subjects and 830 in full-term subjects

hSBA antibody titer ≥ 1:4 and ≥ 1:8 after the 4th dose

In the PPAS3, the number and percentage of subjects with hSBA titer ≥ 1:4 and ≥ 1:8 at D0 before the 4th dose and at D30 after the 4th dose at the 12-month vaccinations (Group 1a) and the 15-month vaccinations (Group 1b) were comparable between preterm and full-term subjects for all serogroups (Table 33).

At D0 before the 4th dose, the percentage of subjects with

• hSBA titers ≥ 1:4 ranged

o From 77.8% (for serogroup A in Group 1b) to 100% (for serogroups Y and W in Group 1a) in preterm subjects and

o From 83.8% (for serogroup A in Group 1a) to 99.2% (for serogroups Y and W in Group 1b) in full-term subjects.

• hSBA titers ≥ 1:8 ranged

o From 55.6% (for serogroup A in Group 1b) to 100% (for serogroups Y and W in Group 1a) in preterm subjects and

o From 56.3% (for serogroup A in Group 1b) to 96.9% (for serogroup W in Group 1a) in full-term subjects

At D30 after the 4th dose, the percentage of subjects with

• hSBA titers ≥ 1:4 ranged

o From 89.5% (for serogroup A in Group 1b) to 100% (for serogroups C, Y and W in both groups) in preterm subjects and

o From 91.4% (for serogroup A in Group 1a) to 100% (for serogroup W in Group 1b) in full-term subjects

• hSBA titers ≥ 1:8 ranged

o From 84.2% (for serogroup A in Group 1b) to 100% (for serogroups C, Y and W in both groups) in preterm subjects and

o From 87.6% (for serogroup A in Group 1a) to 100% (for serogroup W in Group 1b) in full-term subjects

hSBA antibody titer ≥ 4-fold rise from pre- to post-4th dose

In the PPAS3, the number and percentage of subjects with ≥ 4-fold rise of hSBA titers from pre-4th dose to post-4th dose at the 12-month vaccinations (Group 1a) and at the 15-month vaccinations (Group 1b) were comparable between preterm and full-term subjects for all serogroups (Table 34):

• For serogroup A:

o In Group 1a: 62.9% in preterm subjects and 66.5% in full-term subjects

o In Group 1b: 76.5% in preterm subjects and 74.9% in full-term subjects

• For serogroup C:

o In Group 1a: 89.7% in preterm subjects and 90.4% in full-term subjects

o In Group 1b: 88.2% in preterm subjects and 90.9% in full-term subjects

• For serogroup Y:

o In Group 1a: 73.0% in preterm subjects and 80.7% in full-term subjects

o In Group 1b: 83.3% in preterm subjects and 83.1% in full-term subjects

• For serogroup W:

o In Group 1a: 78.4% in preterm subjects and 80.5% in full-term subjects

o In Group 1b: 88.2% in preterm subjects and 90.5% in full-term subjects

Table 27: Summary of geometric means of hSBA titers by preterm and full-term at D0 before and D30 after the 4th dose vaccinations for groups 1a and 1b – Pre-Protocol Analysis Set 3

		Preterm						Full-term					
		Group 1a (N=41)			Group 1b (N=20)			Group 1a (N=634)			Group 1b (N=288)		
Serogroup	Time Point	M	GMT	95% CI	M	GMT	95% CI	M	GMT	95% CI	M	GMT	95% CI
A	D0 before 4th dose	38	9.43	(6.06 ; 14.7)	18	6.60	(4.12 ; 10.6)	569	10.7	(9.58 ; 12.0)	254	8.13	(7.08 ; 9.35)
	D30 after 4th dose	36	40.3	(23.4 ; 69.4)	19	33.2	(15.5 ; 70.9)	606	69.2	(59.6 ; 80.3)	264	83.0	(68.1 ; 101)
C	D0 before 4th dose	40	52.9	(34.5 ; 81.0)	20	40.8	(17.1 ; 97.3)	572	61.9	(54.7 ; 70.1)	262	41.4	(34.1 ; 50.2)
	D30 after 4th dose	39	436	(286 ; 666)	17	512	(224 ; 1170)	616	697	(621 ; 782)	275	664	(561 ; 785)
Y	D0 before 4th dose	38	43.6	(31.5 ; 60.4)	20	32.0	(17.3 ; 59.1)	573	43.5	(39.5 ; 47.8)	263	43.3	(37.8 ; 49.7)
	D30 after 4th dose	39	285	(191 ; 425)	18	287	(171 ; 483)	612	297	(268 ; 329)	277	375	(324 ; 434)
W	D0 before 4th dose	40	52.9	(37.8 ; 74.1)	19	42.8	(19.8 ; 92.9)	579	58.3	(52.8 ; 64.4)	263	59.0	(50.7 ; 68.6)
	D30 after 4th dose	37	365	(243 ; 549)	18	724	(345 ; 1519)	614	389	(352 ; 429)	271	830	(695 ; 991)

N : number of subjects in per-protocol analysis set 3
M: number of subjects with valid serology results for the particular serogroup and time point
Group 1a: MenACYW conjugate vaccine and routine vaccines at 2, 4, 6, and 12 to 15 months of age
Group 1b: MenACYW conjugate vaccine at 2, 4, 6, and 15 to18 months of age and routine vaccines at 2, 4, 6, 12 to 15 months of age
Preterm infant born at gestational age <37 weeks ; full-term infant born at gestational age >=37 weeks
For one subject, gestational age was not collected.

Table 28: Subject with hSBA titer >=1:4 and >=1:8 by preterm and full-term at D0 before and D30 after the 4th-dose vaccinations for groups 1a and 1b – Per-Protocol Analysis Set 3

			Preterm						Full-term					
			Group 1a (N=41)			Group 1b (N=20)			Group 1a (N=634)			Group 1b (N=288)		
Serogroup	Time Point	hSBA Titers	n/M	%	95% CI	n/M	%	95% CI	n/M	%	95% CI	n/M	%	95% CI
A	D0 before 4th dose	>=1:4	30/38	78.9	(62.7 ; 90.4)	14/18	77.8	(52.4 ; 93.6)	477/569	83.8	(80.5 ; 86.8)	213/254	83.9	(78.7 ; 88.2)
		>=1:8	22/38	57.9	(40.8 ; 73.7)	10/18	55.6	(30.8 ; 78.5)	359/569	63.1	(59.0 ; 67.1)	143/254	56.3	(50.0 ; 62.5)
	D30 after 4th dose	>=1:4	33/36	91.7	(77.5 ; 98.2)	17/19	89.5	(66.9 ; 98.7)	554/606	91.4	(88.9 ; 93.5)	257/264	97.3	(94.6 ; 98.9)
		>=1:8	32/36	88.9	(73.9 ; 96.9)	16/19	84.2	(60.4 ; 96.6)	531/606	87.6	(84.7 ; 90.1)	246/264	93.2	(89.4 ; 95.9)
C	D0 before 4th dose	>=1:4	38/40	95.0	(83.1 ; 99.4)	18/20	90.0	(68.3 ; 98.8)	548/572	95.8	(93.8 ; 97.3)	237/262	90.5	(86.2 ; 93.7)
		>=1:8	37/40	92.5	(79.6 ; 98.4)	16/20	80.0	(56.3 ; 94.3)	533/572	93.2	(90.8 ; 95.1)	226/262	86.3	(81.5 ; 90.2)
	D30 after 4th dose	>=1:4	39/39	100	(91.0 ; 100)	17/17	100	(80.5 ; 100)	613/616	99.5	(98.6 ; 99.9)	274/275	99.6	(98.0 ; 100)
		>=1:8	39/39	100	(91.0 ; 100)	17/17	100	(80.5 ; 100)	612/616	99.4	(98.3 ; 99.8)	273/275	99.3	(97.4 ; 99.9)
Y	D0 before 4th dose	>=1:4	38/38	100	(90.7 ; 100)	18/20	90.0	(68.3 ; 98.8)	566/573	98.8	(97.5 ; 99.5)	261/263	99.2	(97.3 ; 99.9)
		>=1:8	38/38	100	(90.7 ; 100)	18/20	90.0	(68.3 ; 98.8)	550/573	96.0	(94.0 ; 97.4)	253/263	96.2	(93.1 ; 98.2)
	D30 after 4th dose	>=1:4	39/39	100	(91.0 ; 100)	18/18	100	(81.5 ; 100)	609/612	99.5	(98.6 ; 99.9)	275/277	99.3	(97.4 ; 99.9)
		>=1:8	39/39	100	(91.0 ; 100)	18/18	100	(81.5 ; 100)	606/612	99.0	(97.9 ; 99.6)	275/277	99.3	(97.4 ; 99.9)
W	D0 before 4th dose	>=1:4	40/40	100	(91.2 ; 100)	17/19	89.5	(66.9 ; 98.7)	572/579	98.8	(97.5 ; 99.5)	261/263	99.2	(97.3 ; 99.9)
		>=1:8	40/40	100	(91.2 ; 100)	17/19	89.5	(66.9 ; 98.7)	561/579	96.9	(95.1 ; 98.1)	252/263	95.8	(92.6 ; 97.9)
	D30 after 4th dose	>=1:4	37/37	100	(90.5 ; 100)	18/18	100	(81.5 ; 100)	611/614	99.5	(98.6 ; 99.9)	271/271	100	(98.6 ; 100)
		>=1:8	37/37	100	(90.5 ; 100)	18/18	100	(81.5 ; 100)	610/614	99.3	(98.3 ; 99.8)	271/271	100	(98.6 ; 100)

N: number of subjects in per-protocol analysis set 3
M: number of subjects with valid serology results for the particular serogroup and time point
Percentages are based on M
n: number of subjects experiencing the endpoint listed in the first 3 columns
Group 1a: MenACYW conjugate vaccine and routine vaccines at 2, 4, 6, and 12 to 15 months of age
Group 1b: MenACYW conjugate vaccine at 2, 4, 6, and 15 to18 months of age and routine vaccines at 2, 4, 6, 12 to 15 months of age
Preterm infant born at gestational age <37 weeks ; full-term infant born at gestational age >=37 weeks
For one subject, gestational age was not collected.

Table 29: Subjects with >= 4-fold rise of hSBA titer by birth timing from pre-4th dose to post – 4th dose for groups 1a and 1b – Per-Protocol analysis set 3

	Preterm						Full-term					
	Group 1a (N=41)			Group 1b (N=20)			Group 1a (N=634)			Group 1b (N=288)		
Serogroup	n/M	%	95% CI	n/M	%	95% CI	n/M	%	95% CI	n/M	%	95% CI
A	22/35	62.9	(44.9 ; 78.5)	13/17	76.5	(50.1 ; 93.2)	367/552	66.5	(62.4 ; 70.4)	179/239	74.9	(68.9 ; 80.3)
C	35/39	89.7	(75.8 ; 97.1)	15/17	88.2	(63.6 ; 98.5)	506/560	90.4	(87.6 ; 92.7)	231/254	90.9	(86.7 ; 94.2)
Y	27/37	73.0	(55.9 ; 86.2)	15/18	83.3	(58.6 ; 96.4)	452/560	80.7	(77.2 ; 83.9)	211/254	83.1	(77.9 ; 87.5)
W	29/37	78.4	(61.8 ; 90.2)	15/17	88.2	(63.6 ; 98.5)	455/565	80.5	(77.0 ; 83.7)	228/252	90.5	(86.2 ; 93.8)

N: number of subjects in per-protocol analysis set 3, for 2nd year of life vaccinations
M: number of subjects with valid serology results for the particular serogroup and time period; Percentages are based on M
n: number of subjects experiencing the endpoint listed in the first 2 columns and met the criterion
Group 1a: MenACYW conjugate vaccine and routine vaccines at 2, 4, 6, and 12 to 15 months of age
Group 1b: MenACYW conjugate vaccine at 2, 4, 6, and 15 to18 months of age and routine vaccines at 2, 4, 6, 12 to 15 months of age
Preterm infant born at gestational age <37 weeks ; full-term infant born at gestational age >=37 weeks
For one subject, gestational age was not collected.

Subgroup Analysis by Preterm and Full-term Birth Status - Safety

A safety overview after any vaccine injections (overall SafAS) by preterm and full-term birth within Group 1 is presented Table 35. In the overall SafAS for any dose, a total of 133 preterm and 1593 full-term subjects were included in Group 1.

No preterm subject reported an immediate unsolicited AE or an immediate unsolicited AR. One full-term subject (< 0.1%; infantile spitting up) reported an immediate unsolicited AE which was not assessed as an immediate AR.

A comparable proportion of preterm and full-term subjects experienced at least 1 solicited injection site reaction (69.8% and 78.7%, respectively). A total of 64.3% of preterm subjects and 72.3% of full-term subjects had a least 1 solicited injection site reaction after any injection of MenACYW conjugate vaccine.

A comparable proportion of preterm and full-term subjects experienced at least 1 solicited systemic reaction within 7 days after any vaccine injection (73.8% and 80.5%, respectively).

A comparable proportion of preterm and full-term subjects had at least 1 unsolicited AE (47.4% and 54.4%, respectively) and at least 1 unsolicited AR (2.3% and 5.7%, respectively).

No preterm subject reported an AE leading to study discontinuation; there was 1 (< 0.1%) out of 1593 full-term subjects.

During the study including the 6-month follow-up period, a total of 10 preterm subjects (7.5%) and 89 full-term subjects (5.6%) experienced at least 1 SAE. There were 1 preterm subject (0.8%) and 12 full-term subjects (0.8%) with at least 1 AESI. A comparable proportion of preterm and full-term subjects reported at least 1 MAAE (55.6% and 61.3%, respectively).

One death was reported in the full-term group (cardiac arrest after the 2-month vaccinations not related to study vaccine).

Table 30: Safety overview after any vaccine injections by the preterm and full-term birth-Overall Safety Analysis Set for any dose

	Preterm Group 1 (N=133)			Full-term Group 1 (N=1593)		
Subjects experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Within 30 mins after any vaccine injections						
Immediate unsolicited AE	0/133	0	(0 ; 2.7)	1/1593	<0.1	(0 ; 0.3)
Immediate unsolicited AR	0/133	0	(0 ; 2.7)	0/1593	0	(0 ; 0.2)
Solicited reaction from D0 to D7 within solicited period after any vaccine injections	102/126	81.0	(73.0 ; 87.4)	1322/1517	87.1	(85.4 ; 88.8)
Solicited injection site reaction	88/126	69.8	(61.0 ; 77.7)	1192/1515	78.7	(76.5 ; 80.7)
Solicited injection site reaction after injection of MenACYW	81/126	64.3	(55.3 ; 72.6)	1095/1514	72.3	(70.0 ; 74.6)
Solicited systemic reaction	93/126	73.8	(65.2 ; 81.2)	1220/1515	80.5	(78.4 ; 82.5)
Within 30 days after any vaccine injections						
Unsolicited AE	63/133	47.4	(38.7 ; 56.2)	867/1593	54.4	(51.9 ; 56.9)
Unsolicited AR	3/133	2.3	(0.5 ; 6.5)	91/1593	5.7	(4.6 ; 7.0)
Unsolicited non-serious injection site AR related to MenACYW	2/133	1.5	(0.2 ; 5.3)	84/1593	5.3	(4.2 ; 6.5)
Unsolicited non-serious systemic AE	58/133	43.6	(35.0 ; 52.5)	812/1593	51.0	(48.5 ; 53.5)
Unsolicited non-serious systemic AR	1/133	0.8	(0 ; 4.1)	8/1593	0.5	(0.2 ; 1.0)
AE leading to study discontinuation	0/133	0	(0 ; 2.7)	1/1593	<0.1	(0 ; 0.3)
SAE	5/133	3.8	(1.2 ; 8.6)	34/1593	2.1	(1.5 ; 3.0)
Death	0/133	0	(0 ; 2.7)	1/1593	<0.1	(0 ; 0.3)
AESI	0/133	0	(0 ; 2.7)	3/1593	0.2	(0 ; 0.5)
MAAE	44/133	33.1	(25.2 ; 41.8)	645/1593	40.5	(38.1 ; 42.9)
During the study						
SAE	10/133	7.5	(3.7 ; 13.4)	89/1593	5.6	(4.5 ; 6.8)
Death	0/133	0	(0 ; 2.7)	1/1593	<0.1	(0 ; 0.3)
AESI	1/133	0.8	(0 ; 4.1)	12/1593	0.8	(0.4 ; 1.3)
MAAE	74/133	55.6	(46.8 ; 64.2)	976/1593	61.3	(58.8 ; 63.7)

N: number of subjects in overall safety analysis set for any dose; "Unsolicited AE" also includes immediate and serious unsolicited AEs.

"Unsolicited non-serious AE" includes any unsolicited AE that is non- serious ; "Immediate unsolicited AE" is collected only for immediate unsolicited systemic AEs.

AR: Reactions related to study vaccine (MenACYW conjugate vaccine); Unsolicited injection site reactions related to NIMP (routine vaccines) are reported separately

For 4 AEs, the relationship to the exact vaccine (IMP/NIMP) cannot be determined.

Group 1: MenACYW conjugate vaccine and routine pediatric vaccines

Preterm infant born at gestational age <37 weeks ; full-term infant born at gestational age >=37 weeks; For one subject, gestational age was not collected.

2.3.3. Discussion on clinical aspects

Study MET42 was a Phase III, partially modified double-blind, randomized, parallel-group, active controlled, multi-center study to compare the immunogenicity and describe the safety of MenACYW conjugate vaccine and MENVEO (Meningococcal [Serogroups A, C, Y, and W-135] Oligosaccharide Diphtheria CRM197 Conjugate Vaccine) when administered concomitantly with routine paediatric vaccines to healthy infants and toddlers in the US.

The MAH intends to submit the presented data together with data from four other studies in a future variation procedure to support the extension of indication for use of MenQuadfi in individuals from the age of 6 weeks and older. The study population of MET42 included healthy male and female subjects aged 42 to 89 days on the day of the 1st visit, which is considered appropriate to support the intended extension of indication.

For this population a variety of vaccinations are recommended during the first two years of age. The study included concomitant vaccinations with Pentacel (diphtheria-tetanus-acellular pertussis [DTaP]-inactivated poliovirus vaccine [IPV]/Hib vaccine), Prevnar13 (PCV13; pneumococcal vaccine), RotaTeq (rotavirus vaccine), ENGERIX-B (HB vaccine), M-M-R II (measles, mumps, rubella vaccine), VARIVAX (varicella vaccine) and HAVRIX (hepatitis A vaccine). The study was performed in the US and the infant vaccines and their respective schedules are partly representative to recommended infant vaccinations in the EU. In EU, for infants a hexavalent vaccine is usually recommended also including a HepB component. Pentacel is not approved in EU. Although differences to the EU recommendations exist, the results are considered relevant for the EU population.

The proposed objectives are informative for the intended indication and the chosen endpoints and intended analyses are considered appropriate. The sample size is sufficient to perform the intended NI-analyses with sufficient power. The randomization and blinding procedures are acceptable.

In total 2628 subjects were enrolled and 1953 completed the study. The dataset for the evaluation of the immune response to the 4th dose included 1417 subjects (53.9%). The majority of subjects were excluded from the analysis because a valid blood samples/result could not be obtained. The percentage of excluded subjects is similar in all groups but slightly more in the Menveo group. While the reported numbers do not give rise to concerns per se, the Applicant should discuss this also in context with results from other studies at the time of the intended extension of indications. The safety set including subjects that received all 4 vaccinations either with MenACYW or Menveo included 2080 (79.2%) subjects. The percentage of excluded subjects is similar for both groups. The respective dataset is considered sufficient to assess safety in the enrolled population.

Immunogenicity

Immunogenicity was assessed at D0 before the first and 4th dose and 30 days after the 3rd and 4th dose. These timepoints are clinically relevant and are acceptable.

The two co-primary immunogenicity objectives of the study were met:

• The NI of **hSBA seroresponses** to meningococcal serogroups A, C, W, and Y when **4 doses** of MenACYW conjugate vaccine (at 2, 4, 6 and 12 months of age) were administered concomitantly with pediatric routine vaccines compared to 4 doses of MENVEO with pediatric routine vaccines, was demonstrated. The seroresponse rates were 79.4% for serogroup A and above 96% for serogroups C, Y and W.

• The NI of **the percentage of subjects with hSBA Ab titers ≥ 1:8** for meningococcal serogroups A, C, Y, and W 30 days after the administration of the last of **3 doses** of MenACYW conjugate vaccine (at 2, 4, and 6 months of age) compared to 3 doses of MENVEO when given concomitantly with pediatric

routine vaccines to infants and toddlers at 6 to 7 months of age, was demonstrated. The percentages of subjects with hSBA antibody titers ≥ 1:8 were 77.9% for serogroup A and above 98% for serogroups C, Y and W.

For both timepoints the results are numerically higher for MenACYW compared to Menveo.

The Applicant further provided six secondary objectives to further characterize the antibody response of the investigational product MenACYW and the concomitant vaccinations.

In order to further characterize the results after the 4th dose (at 12 months of age, corresponding to PEP 1), geometric mean of hSBA titers (GMTs) against meningococcal serogroups A, C, Y, and W at D0 and D30 after the 4th dose of MenACYW conjugate vaccine were provided. At both timepoints the reported GMTs were higher in subjects vaccinated with MenACYW compared to Menveo for serogroups C, Y and W and comparable for serogroup A. This is also reflected in the percentages of subjects with ≥ 4-fold rise of hSBA titer from pre-4th dose to post-4th dose. Overall, the results are comparable but slightly lower for MenACYW, which can be explained with the higher pre-dose GMTs observed for MenACYW. Nevertheless, both groups showed a high percentages of subjects with ≥ 4-fold rise of hSBA titer. These results also demonstrate the persistence of the immune response elicited by both vaccines, which was higher with MenACYW compared to Menveo. To further support the persistence the Applicant also presented the percentages of subjects with hSBA titers ≥ 1:4 and ≥ 1:8 at D0 before the 4th dose. Those were consistently higher in subjects who received MenACYW compared to Menveo.

Similarly to the data presented for the 4th dose, the Applicant presented data to further characterize the response after the 3rd dose (at 6 months of age, corresponding to PEP 2). The presented GMTs were higher in subjects vaccinated with MenACYW compared to Menveo for all serogroups. The percentages of subjects with hSBA titers ≥ 1:4 was comparable for all serogroups.

Further support for the comparable or higher immune response of MenACYW compared to Menveo was provided by further hSBA seroresponse data at different timepoints, hSBA Ab titers distribution and RCDC. All presented data support the results discussed above.

As additional aspect the Applicant included (secondary objective #6) a comparison of the antibody responses after the 4th dose of MenACYW conjugate vaccine administered at 12 or at 15 months of age (6 months or 9 months after the 3rd dose). The group who received the 4th dose at 15 months of age showed higher (serogroup Y and W) or comparable (serogroup A and C) hSBA GMTs at D30 after the 4th dose. At D30 after the 3rd dose, GMTS were comparable between both groups.

Similarly, comparable results were reported with hSBA antibody titers ≥ 1:4 and ≥ 1:8, seroresponse and the percentage of subjects with ≥ 4-fold rise of hSBA titer both from pre-1st dose to post-4th dose vaccinations and the pre-4th dose to post-4th dose vaccinations.

The Applicant further reported GMTs before the 4th dose at 12 and 15 months of age. The reported GMTs were comparable for serogroup A, Y and W but lower for serogroup C in the group with the 4th dose at 15 months of age. It is assumed the Applicant plans to include a respective claim that a later administration of the 4th dose is possible in the extension of indication variation. The Applicant is therefore advised to add a thorough discussion, why this difference does not present an increased risk in the additional three months for children, who receive the 4th dose at 15 months of age.

The NI of immune responses of the routine paediatric vaccines administered concomitantly with MenACYW conjugate vaccine as compared to MENVEO in infants and toddlers 6 weeks old to 18 months was demonstrated. The Applicant performed tests for NI at different timepoint for different vaccines, which are all acceptable. At D30 after the 6-month vaccinations, NI was demonstrated for vaccinations against Hepatitis B, PRP, Polio, Rotavirus, Pertussis and pneumococcal serotypes. At D30 after the 12-month vaccinations NI was demonstrated for Measles, Mumps, Rubella, Varicella and

pneumococcal serotypes. At D30 after the 15 month-vaccinations NI was demonstrated for PRP, Polia and Pertussis. The provided data even show numerically higher responses in the group receiving MenACYW for many comparisons. In addition, the Applicant provided the respective antibody concentrations/titer and the number of subjects reaching a respective threshold for each of the evaluated vaccines at each timepoint. These data confirm the comparable results between groups vaccinated with MenACYW and Menveo. Only slight differences have been observed, but mainly in numerically higher results in the MenACYW groups.

Overall, it can be concluded that the immune response of the concomitant pediatric vaccines is comparable in the groups receiving MenACYW or Menveo.

Safety

Safety was evaluated as observational objective, which is acceptable. The Applicant distinguished between immediate unsolicited systemic AEs within 30 minutes of each vaccination, solicited AEs from D0 to D07 after each vaccination, unsolicited AEs from D0 to D30 after each vaccination and SAE (including AESIs and MAAEs) throughout the study from Visit 1 until the end of the 6-month follow-up period after the last vaccination. This separation is considered clinically meaningful and is therefore supported.

The Applicant provided the results for the overall study as well as separated for different safety datasets corresponding the different doses. This allows a more detailed assessment of the safety data, which is appreciated.

Overall, the safety profiles of MenACYW and Menveo given concomitantly with other infant vaccines were comparable in all safety datasets.

Immediate unsolicited AEs within 30 minutes occurred only in 2 subjects (1 in the MenACYW and 1 in the Menveo group) during the study. None was related to the vaccines.

Solicited injection site reactions within 7 days following injection were reported in about 78% of subjects in both groups. About 80% reported with solicited systemic reactions. The most frequently reported solicited injection site reactions were tenderness, erythema and swelling. The most frequently reported solicited systemic reactions were irritability, crying abnormal, drowsiness, appetite lost, fever, and vomiting. Most solicited injection site and systemic reactions started within D0 to D3, resolved (spontaneously) after 1-3 days and were of Grade 1 or 2 intensity. For MenACYW conjugate vaccine or MENVEO, about 9% of subjects in each group experienced at least 1 Grade 3 solicited injection site reaction predominantly consisting of tenderness in both groups. At least 1 Grade 3 solicited systemic reaction was reported by ~18% of subjects in both groups predominantly consisting of irritability in both groups.

Unsolicited AEs were reported for about 54% of subjects in both groups and about 6% reported at least 1 unsolicited adverse reaction (AR). Unsolicited AEs were mainly reported in the SOCs: "Infections and infestations", "General disorders and administration site conditions" and "Gastrointestinal disorders". The most frequently reported events were upper respiratory tract infection and injection site bruising.

One subject in the MenACYW and one subject in the Menveo group discontinued due to an AE. Both were not considered to be related to study drug.

The percentage of subjects that experienced serious AEs (within 30 days: ~2%; 6 months follow up: ~5%), AESIs (within 30 days: <0.2%; 6 months follow up: <0.8%) and MAAEs (within 30 days: ~40%; 6 months follow up: ~60%) was also comparable between the MenACYW and Menveo groups.

The most frequently reported SAEs were Febrile convulsion, Bronchiolitis and other infections and infection related AEs.

Two SAEs were assessed as related to study vaccine during the study including the 6-month follow-up period. Both cases occurred within 30 days of vaccination: 1 case of febrile convulsions in Group 1 (assessed as related to study vaccine by the Investigator and as unrelated to study vaccine by the Sponsor). The Sponsor's conclusion that the event is likely to be related to acute concomitant infections can be followed. And 1 case of post-vaccination fever in Group 2 (assessed as related to study vaccine by both the Investigator and the Sponsor). The event occurred 8h after the subject received the study vaccines. The assessment as related to the received vaccines can be followed. However, the event is a known AEs for the administered vaccines and does not represent any new safety signal.

One death occurred during the study. A cardiac arrest with fatal outcome was reported in Group 1 6 days after the 2-month vaccinations (1st dose of MenACYW conjugate vaccine administered concomitantly with Pentacel, Prevnar 13, RotaTeq, and ENGERIX B). This event was assessed as unrelated to the investigational vaccine administered concomitantly with routine pediatric vaccines. The MAH's conclusion that the event was not related to the drug can be followed.

Differences between time points were observed but were similar between groups and do not raise concerns.

Overall, the reported safety profile seems manageable and no new safety signals were identified. As far as applicable, the safety profile is comparable to the safety profile reported in older children as assessed during the initial MAA.

The MAH provided additional subgroup analyses for immunogenicity for gender and race, which did not reveal any difference. Further subgroup analyses of immunogenicity and safety for pre- and full-term infants showed comparable results.

3. CHMP overall conclusion and recommendation

In study MET42 comparable or higher immune response of MenACYW when administered concomitantly with routine paediatric vaccines was observed compared to Menveo when administered concomitantly with routine paediatric vaccines. In addition, it can be concluded that the immune response of the concomitant paediatric vaccines is comparable in the groups receiving MenACYW or Menveo.

The reported safety profile is manageable and no new safety signals were identified. As far as applicable, the safety profile is comparable to the safety profile reported in older children as assessed during the initial MAA.

Currently other studies in this population are still ongoing. The MAH's plan to complete these studies and to submit all the data together under a type II variation with Product Information (PI) update to support the extension of indication for use of MenQuadfi in individuals from the age of 6 weeks and older is supported. Since this submission is planned in Q1 2025 in EU, this is acceptable and no immediate changes to the PI are warranted. For the planned procedure, the MAH is advised to discuss any differences between studies.

☒ Fulfilled:

No further action required.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non clinical studies

Not applicable.

Clinical studies

Product Name: MenQuadfi

Active substance:

Neisseria meningitidis group A polysaccharide

Neisseria meningitidis group C polysaccharide

Neisseria meningitidis group Y polysaccharide

Neisseria meningitidis group W polysaccharide

Conjugated to tetanus toxoid carrier protein

Study title	Study number	Date of completion	Date of submission of final study report
Safety and Immunogenicity of a 3-Dose Schedule of an Investigational Quadrivalent Meningococcal Conjugate Vaccine when Administered Concomitantly with Routine Pediatric Vaccines in Healthy Infants and Toddlers	MET33	18 February 2022	Oct. 2023
Immunogenicity and Safety Study of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Infants and Toddlers when Administered Using a 1+1 Schedule in a National Immunization Schedule Having a Meningococcal Group B Vaccine as Standard of Care	MET52	05 December 2022	Sept. 2023
A Randomized Study to Describe the Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine Administered Concomitantly with Routine Pediatric Vaccines in Healthy Infants and Toddlers	MET41	16 March 2023	Oct. 2023
Immunogenicity and Safety Study of an Investigational Quadrivalent Meningococcal Conjugate Vaccine when Administered Concomitantly with Routine Pediatric Vaccines in Healthy Infants and Toddlers in Europe	MET58	17 May 2023	Q4 2024
Immunogenicity and Safety Study of an Investigational Quadrivalent Meningococcal Conjugate Vaccine when Administered Concomitantly with Routine Pediatric Vaccines in Healthy Infants and Toddlers	MET42	22 September 2023	Q2 2024
Immunogenicity and Safety Study of an Investigational Quadrivalent Meningococcal Conjugate Vaccine Administered Concomitantly with Routine Pediatric Vaccines in Healthy Infants and Toddlers	MET61	20 October 2023	May 2024