Amsterdam, 25 April 2024
EMA/CHMP/146989/2024
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/P46/007.1

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**	**Need for discussion**
☐	Start of procedure	16 Oct 2023	16 Oct 2023	☐
☐	CHMP Rapporteur Assessment Report	20 Nov 2023	20 Nov 2023	☐
☐	CHMP members comments	04 Dec 2023	04 Dec 2023	☐
☐	Updated CHMP Rapporteur Assessment Report	07 Dec 2023	07 Dec 2023	☐
☐	CHMP adoption of conclusions:	14 Dec 2023	14 Dec 2023	☐
☐	Submission	12 Jan 2024	12 Jan 2024	☐
☐	Re-start	24 Jan 2024	24 Jan 2024	☐
☐	CHMP Rapporteur Assessment Report	07 Feb 2024	06 Feb 2024	☐
☐	CHMP members comments	12 Feb 2024	12 Feb 2024	☐
☐	Updated CHMP Rapporteur Assessment Report	15 Feb 2024	15 Feb 2024	☐
☐	CHMP adoption of conclusions:	22 Feb 2024	22 Feb 2024	☐
☐	Submission	26 Mar 2024	21 Mar 2024	☐
☐	Re-start	27 Mar 2024	27 Mar 2024	☐
☐	CHMP Rapporteur Assessment Report	10 Apr 2024	05 Apr 2024	☐
☐	CHMP members comments	15 Apr 2024	15 Apr 2024	☐
☐	Updated CHMP Rapporteur Assessment Report	18 Apr 2024	N/A	☐
☒	CHMP adoption of conclusions:	25 Apr 2024	25 Apr 2024	☐

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1. Introduction

On 2-Oct-2023, the MAH submitted a completed paediatric study for MenQuadfi, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study MET41 "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" 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 weeks to 12 months population: MET33, MET41, MET42, MET52, MET58, MET61) is expected to be submitted by Q1/2025. A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

The formulation of the MenACYW vaccine (MenQuadfi) as solution for injection is approved for the active immunisation of individuals from the age of 12 months and older against invasive meningococcal disease caused by Neisseria (N.) meningitidis serogroups A, C, W, and Y (as 10µg polysaccharides each and with 55µg conjugated tetanus toxoid carrier protein).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study MET41: "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".

2.3.2. Clinical study

Description

MET41 is a phase III, modified double-blind, randomised, parallel-group, active-controlled, multi-centre study to describe the safety of MenACYW conjugate vaccine and the comparator vaccine MENVEO when administered in a 3+1 schedule concomitantly with routine paediatric vaccines given to healthy infants and toddlers between 6 weeks of age and 12 months of age.

This study was conducted at 75 centres that enrolled, screened, and randomised subjects in the United States (US) and Puerto Rico.

The study was conducted between 17-Sep-2018 (first subject first visit) to 16-Mar-2023 (last subject last contact).

Methods

Study participants

Approximately 3080 healthy infants aged ≥ 42 to ≤ 89 days were planned to be randomised.

The study population included healthy male and female subjects aged 42 to 89 days on the day of the first study visit. Subjects had to have received the first dose of hepatitis B vaccine at least 28 days before the first study visit.

Written informed consent was obtained from the subject's parent(s) / guardian.

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 in the 4 weeks before and/or following any study vaccination was not allowed. Subjects should not have received more than 1 dose of hepatitis B vaccine at enrollment.

Treatments

Group 1: MenACYW conjugate vaccine + routine paediatric vaccines

Group 2: MENVEO + routine paediatric vaccines

All subjects were to receive a dose of either MenACYW conjugate vaccine or MENVEO with the following routine paediatric vaccines:

- PENTACEL (diphtheria, tetanus, and acellular pertussis-inactivated poliovirus //*Haemophilus influenzae* type b [DTaP-IPV//Hib]) at 2, 4, and 6 months of age;
- PREVNAR 13 (pneumococcal 13-valent conjugate vaccine; PCV13) at 2, 4, 6, and 12 months of age;
- RotaTeq (rotavirus vaccine) at 2, 4, and 6 months of age;
- ENGERIX-B (hepatitis B vaccine) at 2 and 6 months of age[1]; and
- M-M-R II (measles, mumps, and rubella vaccine) and VARIVAX (varicella vaccine) at 12 months of age.

All subjects were to complete the last study visit at 13 to 14 months of age. For all subjects, the 4th dose of PENTACEL was to be administered by site personnel at 15 to 18 months of age as per standard practice. The 4th dose of PENTACEL was to be provided by the Sponsor for completion of the DTaP series with vaccine from the same manufacturer, to ensure compliance with the Advisory Committee on Immunization Practices (ACIP) recommendation.

Study vaccines were to be administered as part of the study on the following **schedules**:

Group 1: MenACYW conjugate vaccine and routine paediatric vaccines at 2, 4, 6, and 12 months of age

Group 2: MENVEO and routine paediatric vaccines at 2, 4, 6, and 12 months of age

Table 1: Vaccination schedule– Study MET41

Visit/Contact	Visit 1	Visit 2	Visit 3	Visit 4
Age of Subject	2 months	4 months	6 months	12 months
Group 1	MenACYW DTaP-IPV//Hib PCV13 Rotavirus Hep B	MenACYW DTaP-IPV//Hib PCV13 Rotavirus	MenACYW DTaP-IPV//Hib PCV13 Rotavirus Hep B	MenACYW PCV13 MMR Varicella
Group 2	MENVEO® DTaP-IPV//Hib PCV13 Rotavirus Hep B	MENVEO® DTaP-IPV//Hib PCV13 Rotavirus	MENVEO® DTaP-IPV//Hib PCV13 Rotavirus Hep B	MENVEO® PCV13 MMR Varicella
DTaP-IPV//Hib: PENTACEL®; PCV13: PREVNAR 13®; Rotavirus: RotaTeq®; Hep B: ENGERIX-B®; MMR: M-M-R® II; Varicella: VARIVAX®				

Objective

The objective was to **describe the safety profile** of **MenACYW conjugate vaccine and MENVEO when administered concomitantly with routine paediatric vaccines** in healthy infants and toddlers.

Safety outcomes were described in the following manner:

- For the overall population for any vaccine injection
- After the first MenACYW conjugate vaccine dose at 2 months of age
- After the second MenACYW conjugate vaccine dose at 4 months of age
- After the third MenACYW conjugate vaccine dose at 6 months of age
- After the fourth MenACYW conjugate vaccine dose at 12 months of age
- For the subjects who received all 4 doses of MenACYW conjugate vaccine

Outcomes/endpoints

Safety endpoints and time windows for collection are summarized in Table 2. Safety results were described in the clinical study report (CSR) for subjects in all study groups after vaccination at 2, 4, 6, and 12 months of age (Visit 1, Visit 2, Visit 3, and Visit 4, respectively).

Table 2: Safety endpoints and time windows for collection – Study MET41

Safety Parameter	Data Collected and Collection Window
Immediate Unsolicited systemic adverse events (AEs)/adverse reactions* (ARs)	Occurrence within 0-30 minutes after each vaccination by nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term [PT]), duration, intensity, and relationship to vaccination, and whether the event led to early termination from the study
Solicited (pre-defined) Injection Site Reactions	Occurrence within 7 days after vaccination (D0 to D07) by time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study
Solicited (pre-defined) Systemic Reactions	Occurrence within 7 days after vaccination (D0 to D07) by time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study
Unsolicited non-serious AEs/ARs	Occurrence within 30 days after vaccination (D0 to D30), nature (MedDRA PT), time of onset, duration, intensity, action taken, relationship to vaccination, and whether the event led to early termination from the study
Adverse Events of Special Interest (AESI)	Occurrence throughout the trial from Visit 1 to the 6-month follow-up contact after the last vaccination, nature (MedDRA PT), time of onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the event led to early termination from the study
Serious Adverse Events (SAEs): All and related	Occurrence throughout the trial from Visit 1 to the 6-month follow-up contact after the last vaccination, nature (MedDRA PT), time of onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the event led to early termination from the study
Deaths	Occurring throughout the trial period
Medically-attended adverse events (MAAEs)	Occurrence throughout the trial from Visit 1 to the 6-month follow-up contact after the last vaccination, nature (MedDRA PT), time of onset, duration, intensity, action taken, relationship to vaccination, and whether the event led to early termination from the study

*An AE is considered an adverse reaction (AR) when a causal relationship between the vaccine and an AE are at least a reasonable possibility.

Sample size

Approximately 3080 healthy infants were planned to be randomised.

The sample size of this study was chosen to provide safety data; it was not intended for the purposes of hypothesis testing. No formal sample size calculation was performed. Though there were no statistically powered hypotheses, the overall study cohort of 3080 subjects were to provide a probability of approximately 95% of observing any adverse events (AE) with a true incidence of 0.15%. In the treatment arm with 2310 subjects, there was a probability of approximately 95% of observing any AE with a true incidence of 0.2%.

Randomisation and blinding (masking)

Randomisation

All subjects were centrally assigned to randomised study intervention using an Interactive Response Technology (IRT).

On the day of enrollment, subjects who meet the inclusion/exclusion criteria and whose parent / guardian signs the informed consent form (ICF) will be randomly assigned to Group 1 or Group 2 in a 3:1 ratio such that Group 1 will have approximately 2310 subjects and Group 2 will have approximately 770 subjects.

Site staff will connect to the IRT system, enter the identification and security information, and confirm a minimal amount of data in response to IRT system prompts. The IRT system will then provide the vaccine assignment and subject number. The full detailed procedures for group allocation are described in the Operating Guidelines. If the subject is not eligible to participate in the study, then the information will only be recorded on the subject recruitment log.

Subject numbers that are assigned by the IRT system will consist of a 12-digit string (a 3-digit country identifier, a 4-digit study centre identifier, and a 5-digit subject identifier). For example, Subject 840000100005 is the fifth subject enrolled in Centre Number 1 in the US (840 being the US country code).

Subject numbers should not be reassigned for any reason. The randomisation codes will be kept securely in the IRT system.

Blinding

This trial is a modified double-blind trial, which means that the subject's parent / guardian, the Investigator, and other study personnel remain unaware of the treatment assignments throughout the trial. An unblinded vaccine administrator will administer the appropriate vaccine but will not be involved in safety data collection. The Sponsor will also remain blinded to treatment assignments throughout the trial until database lock.

The code may be broken in the event of an AE only when the identification of the vaccine received could influence the treatment of the subject. Code-breaking should be limited to the subject(s) experiencing the AE.

- The blind can be broken by the Investigator or a delegate through the IRT system, as explained in the code-breaking procedures described in the Operating Guidelines. Once the emergency has been addressed by the site, the Investigator or a delegate must notify the Sanofi Pasteur RMO if a subject's code was broken. All contact attempts with the Sponsor prior to unblinding are to be documented in the source documents, and the code breaking CRF is to be completed.

A request for the code to be broken may also be made:

- by the Global pharmacovigilance (GPV) Department through an internal system for reporting to health authorities in the case of an SAE as described in International Conference on Harmonisation (ICH) E2A. In this case, the code will be broken only for the subject(s) in question. The information resulting from code-breaking (i.e., the subject's vaccine or group assignment) will not be communicated to either the Investigator or the immediate team working on the study, except for the GPV representative.

The Independent Ethics Committee (IEC) / Institutional Review Board (IRB) must be notified of the code-breaking. All documentation pertaining to the event must be retained in the site's study records and in the Sanofi Pasteur files. Any intentional or unintentional code-breaking must be reported, documented, and explained, and the name of the person who requested it must be provided to the Sponsor.

Statistical Methods

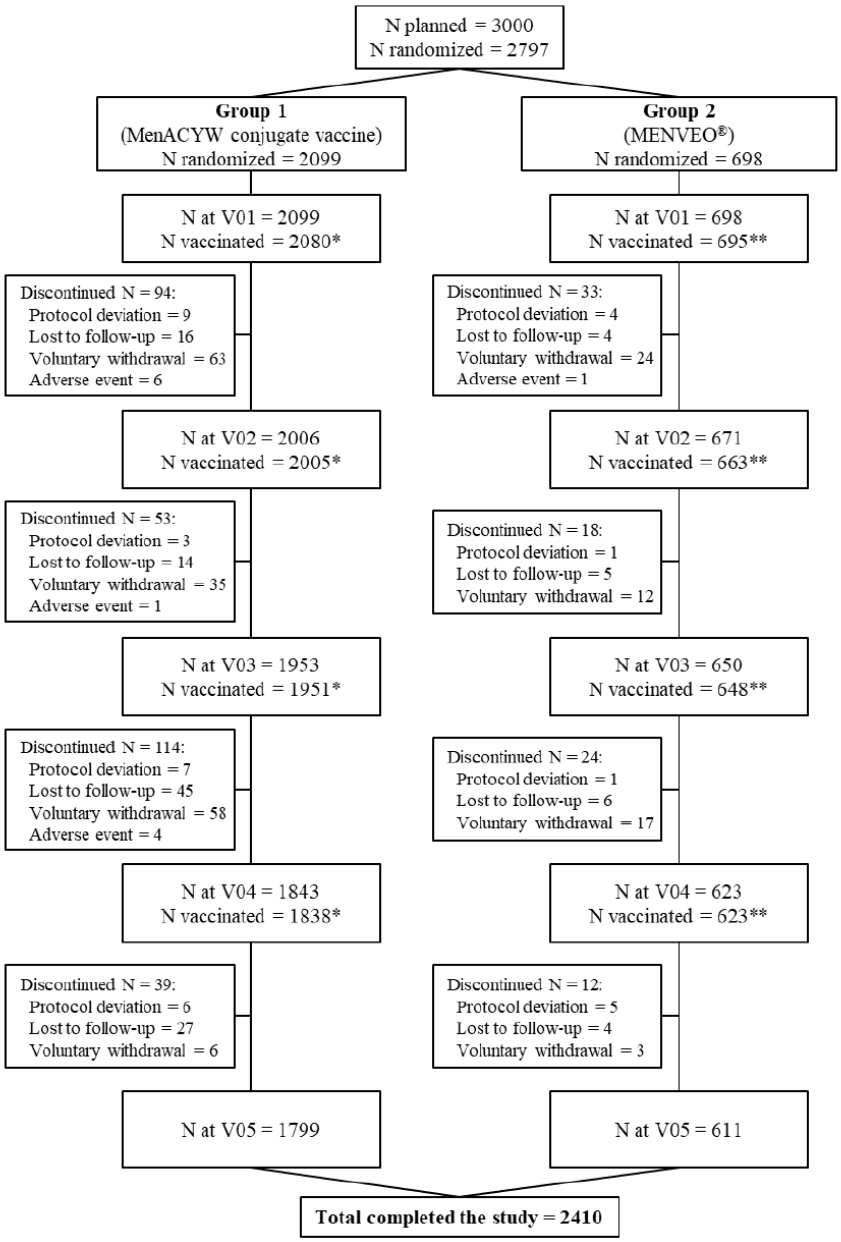
No hypotheses were tested. Descriptive statistics were presented.

Results

Participant flow

A total of 2797 subjects were enrolled and randomised in the study: 2099 subjects were randomised to Group 1 and 698 subjects were randomised to Group 2. A total of 1799 (85.7%) subjects in Group 1 and 611 (87.5%) subjects in Group 2 completed the study. A subject disposition flow chart is provided in Figure 1. A summary of disposition/vaccine allocation for randomised subjects is presented in Table 3.

Figure 1: Subject disposition flow chart



V: visit
N vaccinated: subjects vaccinated with MenACYW conjugate vaccine (Group 1) or MENVEO® (Group 2)
* Subjects who received MenACYW conjugate vaccine
** Subjects who received MENVEO®

Table 3: Disposition by randomised group – All randomised subjects

Age/Dose#	Visit Timepoint		Group 1 (N=2099) n (%)	Group 2 (N=698) n (%)	All (N=2797) n (%)
2 Months (Dose 1)	V01	Randomized	2099 (100)	698 (100)	2797 (100)
		Received MenACYW	2080 (99.1)	0	2080 (74.4)
		Received MENVEO	2 (<0.1)	695 (99.6)	697 (24.9)
		Received PENTACEL	2082 (99.2)	695 (99.6)	2777 (99.3)
		Received PREVNAR 13	2082 (99.2)	695 (99.6)	2777 (99.3)
		Received RotaTeq	2082 (99.2)	695 (99.6)	2777 (99.3)
		Received ENGERIX-B	2082 (99.2)	695 (99.6)	2777 (99.3)
4 Months (Dose 2)	V02	Present	2006 (95.6)	671 (96.1)	2677 (95.7)
		Received MenACYW	2005 (95.5)	1 (0.1)	2006 (71.7)
		Received MENVEO	0	663 (95.0)	663 (23.7)
		Received PENTACEL	2004 (95.5)	664 (95.1)	2668 (95.4)
		Received PREVNAR 13	2004 (95.5)	664 (95.1)	2668 (95.4)
		Received RotaTeq	2004 (95.5)	664 (95.1)	2668 (95.4)
6 Months (Dose 3)	V03	Present	1953 (93.0)	650 (93.1)	2603 (93.1)
		Received MenACYW	1951 (92.9)	0	1951 (69.8)
		Received MENVEO	0	648 (92.8)	648 (23.2)
		Received PENTACEL	1948 (92.8)	647 (92.7)	2595 (92.8)
		Received PREVNAR 13	1948 (92.8)	647 (92.7)	2595 (92.8)
		Received RotaTeq	1947 (92.8)	647 (92.7)	2594 (92.7)
		Received ENGERIX-B	1947 (92.8)	647 (92.7)	2594 (92.7)
12 Months (Dose 4)	V04	Present	1843 (87.8)	623 (89.3)	2466 (88.2)
		Received MenACYW	1838 (87.6)	0	1838 (65.7)
		Received MENVEO	0	623 (89.3)	623 (22.3)
		Received M-M-R II	1827 (87.0)	618 (88.5)	2445 (87.4)
		Received VARIVAX	1830 (87.2)	618 (88.5)	2448 (87.5)
		Received PREVNAR 13	1832 (87.3)	620 (88.8)	2452 (87.7)

n: number of subjects fulfilling the item listed.
N: total number of subjects randomized in each study group.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.
Group 2: MENVEO® vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.

Recruitment

This study was conducted at 75 centres that enrolled, screened, and randomised subjects in the US and Puerto Rico.

- Study initiation date (first subject first visit): 17 September 2018.
- Study completion date (last subject last contact): 16 March 2023.
- Vaccination period: 17 September 2018 to 14 October 2022.
- Database lock: 21 June 2023.

Baseline data

A summary of baseline demographics for all randomised subjects is presented in Table 4. Overall, 2797 subjects were enrolled (1463 males [52.3%] and 1334 females [47.7%]). There were more males than females in both vaccination groups. The male/female ratio was 1.10 in Group 1 and the male/female ratio was 1.08 in Group 2. The mean age of the subjects at enrollment was 64.7 (±6.63) days in Group 1 and 64.9 (±6.77) days in Group 2 (Table 2). Most subjects were White (82.2%), followed by Black or African American subjects (9.9%). The majority of subjects were Not Hispanic or Latino (72.4% of subjects).

Table 4: Baseline demographics by randomised group – All randomised subjects

	Group 1 (N=2099)	Group 2 (N=698)	All (N=2797)
Sex: n (%)			
Male	1101 (52.5)	362 (51.9)	1463 (52.3)
Female	998 (47.5)	336 (48.1)	1334 (47.7)
Sex ratio: Male/Female	1.10	1.08	1.10
Age: (Days)			
M	2099	698	2797
Mean (SD)	64.7 (6.63)	64.9 (6.77)	64.7 (6.67)
Min ; Max	42.0 ; 89.0	42.0 ; 89.0	42.0 ; 89.0
Median	63.0	63.0	63.0
Q1 ; Q3	61.0 ; 67.0	61.0 ; 67.0	61.0 ; 67.0
Racial origin: n (%)			
White	1719 (81.9)	580 (83.1)	2299 (82.2)
Asian	28 (1.3)	12 (1.7)	40 (1.4)
Black or African American	210 (10.0)	67 (9.6)	277 (9.9)
American Indian or Alaska Native	8 (0.4)	0	8 (0.3)
Native Hawaiian or Other Pacific Islander	10 (0.5)	5 (0.7)	15 (0.5)
Mixed Origin	102 (4.9)	31 (4.4)	133 (4.8)
Unknown	12 (0.6)	0	12 (0.4)
Not Reported	10 (0.5)	3 (0.4)	13 (0.5)
Ethnicity: n (%)			
Hispanic or Latino	566 (27.0)	197 (28.2)	763 (27.3)
Not Hispanic or Latino	1526 (72.7)	499 (71.5)	2025 (72.4)
Unknown	0	0	0
Not Reported	7 (0.3)	2 (0.3)	9 (0.3)

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 M.
Q1; Q3: first quartile; third quartile.
SD: standard deviation.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.
Group 2: MENVEO® vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.

Number analysed

Definition of the 6 Safety Analysis Sets

Safety Analysis Set (SafAS) Overall Population: Defined as those subjects who have received at least 1 dose of the study vaccines and have any safety data available. All subjects had their safety analysed after any dose according to the vaccine received at the first dose.

- SafAS1: Defined as those subjects who have received the study vaccine at Visit 1 around 2 months of age and have any safety data available. All subjects had their safety analysed after the Visit 1 dose according to the vaccine they actually received at Visit 1.
- SafAS2: Defined as those subjects who have received the study vaccine at Visit 2 around 4 months of age and have any safety data available. All subjects had their safety analysed after this dose according to the vaccine they actually received at Visit 2.
- SafAS3: Defined as those subjects who have received the study vaccine at Visit 3 around 6 months of age and have any safety data available. All subjects had their safety analysed after the dose according to the vaccine they actually received at Visit 3.
- SafAS4: Defined as those subjects who have received the study vaccine at Visit 4 around 12 months of age and have any safety data available. All subjects had their safety analysed after the dose according to the vaccine they actually received at Visit 4.
- SafAS5: Defined as those subjects who have received all 4 doses of the study vaccine (3 doses in infancy and 1 dose in the second year of life at 12 months of age) and have any safety data available. All 4-dose vaccinations received in a series should be either all MenACYW conjugate vaccine or all MENVEO.

Table 5: Safety analysis set by vaccination group - All randomised subjects

	Group 1 (N=2080) n (%)	Group 2 (N=697) n (%)	Randomized but not vaccinated (N=20) n (%)	All (N=2797) n (%)
Subjects received vaccine	2080 (100)	697 (100)	-	2777 (99.3)
Overall safety analysis set for any dose	2080 (100)	697 (100)	-	2777 (99.3)
Safety analysis set for vaccination at 2 months of age	2080 (100)	697 (100)	-	2777 (99.3)
Safety analysis set for vaccination at 4 months of age	2006 (96.4)	663 (95.1)	-	2669 (95.4)
Safety analysis set for vaccination at 6 months of age	1951 (93.8)	648 (93.0)	-	2599 (92.9)
Safety analysis set for vaccination at 12 months of age	1838 (88.4)	623 (89.4)	-	2461 (88.0)
Safety analysis set for all 4-dose vaccination*	1836 (88.3)	622 (89.2)	-	2458 (87.9)

n: number of subjects experiencing the endpoint;
"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: MenACYW conjugate vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.
Group 2: MENVEO ® vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.

Exposure

A total of 2797 subjects were randomised: 2099 subjects to Group 1 and 698 to Group 2. Overall, a total of 2777 subjects received at least one dose of study vaccine, 2080 subjects in Group 1 and 697 in Group 2.

At Visit 1, a total of 2797 subjects (100%) were present: 2099 subjects (100%) in Group 1 and 698 subjects (100%) in Group 2. A total of 2080 subjects (99.1%) received MenACYW conjugate vaccine in Group 1. A total of 697 subjects received MENVEO: 2 subjects (< 0.1%) randomised in Group 1 and 695 subjects (99.6%) randomised in Group 2. A total of 2777 subjects (99.3%) received PENTACEL, PREVNAR 13, RotaTeq, and ENGERIX-B: 2082 subjects (99.2%) in Group 1 and 695 subjects (99.6%) in Group 2.

At Visit 2, a total of 2677 subjects (95.7%) were present: 2006 subjects (95.6%) in Group 1 and671 subjects (96.1%) in Group 2. A total of 2005 subjects (95.5%) randomised in Group 1 and 1 subject (0.1%) randomised in Group 2 received MenACYW conjugate vaccine. A total of 663 subjects (95.0%) received MENVEO in Group 2. A total of 2668 subjects (95.4%) received PENTACEL, PREVNAR 13, and RotaTeq: 2004 subjects (95.5%) in Group 1 and 664 subjects (95.1%) in Group 2.

At Visit 3, a total of 2603 subjects (93.1%) were present: 1953 subjects (93.0%) in Group 1 and 650 subjects (93.1%) in Group 2. A total of 1951 subjects (92.9%) received MenACYW conjugate vaccine

in Group 1. A total of 648 subjects (92.8%) received MENVEO in Group 2. A total of 2595 subjects (92.8%) received PENTACEL and PREVNAR 13: 1948 subjects (92.8%) in Group 1 and 647 subjects (92.7%) in Group 2. A total of 2594 subjects (92.7%) received RotaTeq and ENGERIX-B: 1947 subjects (92.8%) in Group 1 and 647 subjects (92.7%) in Group 2.

At Visit 4, a total of 2466 subjects (88.2%) were present: 1843 subjects (87.8%) in Group 1 and 623 subjects (89.3%) in Group 2. A total of 1838 subjects (87.8%) received MenACYW conjugate vaccine in Group 1. A total of 623 subjects (89.3%) received MENVEO in Group 2. A total of 2452 subjects (87.7%) received PREVNAR 13: 1832 subjects (87.3%) in Group 1 and 620 subjects (88.8%) in Group 2. A total of 2448 subjects (87.5%) received VARIVAX: 1830 subjects (87.2%) in Group 1 and 618 subjects (88.5%) in Group 2. A total of 2445 subjects (87.4%) received M-M-R II: 1827 subjects (87.0%) in Group 1 and 618 subjects (88.5%) in Group 2.

Study Discontinuation

Table 6: Study subjects with early termination by randomised group - Randomised study subjects

	Group 1 (N=2099) n (%)	Group 2 (N=698) n (%)	All (N=2797) n (%)
Completed	1799 (85.7)	611 (87.5)	2410 (86.2)
Early termination	300 (14.3)	87 (12.5)	387 (13.8)
Reason			
Adverse Event *	11 (0.5)	1 (0.1)	12 (0.4)
Protocol Deviation	25 (1.2)	11 (1.6)	36 (1.3)
Withdrawal by Parent/Guardian	162 (7.7)	56 (8.0)	218 (7.8)
Lost to Follow-Up	102 (4.9)	19 (2.7)	121 (4.3)

n: number of study subjects fulfilling the item listed
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.
Group 2: MENVEO® vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.
*Discontinuations for adverse events may not be considered at the time of the safety analysis if intensity is < Grade 1 according to the Sponsor.

Study conduct

Table 7: Major and critical protocol deviations by randomised group – Randomised study subjects

	Group 1 (N=2099) n (%)	Group 2 (N=698) n (%)	All (N=2797) n (%)
Study participants with at least one major or critical protocol deviation	781 (37.2)	241 (34.5)	1022 (36.5)
Study participants with at least one major protocol deviation	780 (37.2)	241 (34.5)	1021 (36.5)
Informed consent obtained with an error in consent process or documentation	3 (0.1)	2 (0.3)	5 (0.2)
Healthy infants as determined by medical history, physical examination and judgment of the Investigator.	9 (0.4)	0	9 (0.3)
Subject and parent/guardian are able to attend all scheduled visits and to comply with all trial procedures	1 (<0.1)	0	1 (<0.1)
Infants who received the first dose of hepatitis B vaccine at least 28 days before the first study visit	1 (<0.1)	0	1 (<0.1)
Participation at the time of study enrollment or in the 4 weeks preceding the first trial vaccination or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure	2 (<0.1)	0	2 (<0.1)
Receipt of more than 1 previous dose of hepatitis B vaccine	3 (0.1)	0	3 (0.1)
Receipt of immune globulins, blood, or blood-derived products since birth	0	1 (0.1)	1 (<0.1)
History of diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, hepatitis A, measles, mumps, rubella, varicella; and of Haemophilus influenzae type b, Streptococcus pneumoniae, and /or rotavirus infection or disease	1 (<0.1)	0	1 (<0.1)
Protocol-specified co-administered routine vaccine not received	276 (13.1)	82 (11.7)	358 (12.8)
Protocol specified co-administered routine vaccine was administered but not within the protocol-specified time window	48 (2.3)	9 (1.3)	57 (2.0)
Protocol-specified co-administered routine vaccine was administered but not as per protocol	10 (0.5)	1 (0.1)	11 (0.4)
Subject received an unacceptable protocol specified co-administered routine vaccine for use	8 (0.4)	5 (0.7)	13 (0.5)
Study visit, telephone call or safety contact was not performed	314 (15.0)	88 (12.6)	402 (14.4)
Study visit, telephone call or safety contact was not performed within the protocol-specified time window	254 (12.1)	69 (9.9)	323 (11.5)
Study visit, telephone call or safety contact not performed as defined in the protocol	60 (2.9)	20 (2.9)	80 (2.9)
Study procedure performed by unqualified / unauthorized personnel	2 (<0.1)	0	2 (<0.1)
IMP was not administered	261 (12.4)	75 (10.7)	336 (12.0)
IMP was administered but not as per protocol	2 (<0.1)	1 (0.1)	3 (0.1)
IMP was administered but not within the protocol-specified time window	301 (14.3)	83 (11.9)	384 (13.7)
Subject/ patient received an unacceptable IMP for use	12 (0.6)	4 (0.6)	16 (0.6)
IMP number actually given to the subject is different from the IMP number allocated by the randomization process	6 (0.3)	1 (0.1)	7 (0.3)
Erroneous subject's diary card given to the subject	2 (<0.1)	0	2 (<0.1)
Failure to report AESI/SAE to sponsor within the protocol-specified time window (ex 24h for SAE and AESI)	5 (0.2)	1 (0.1)	6 (0.2)
Failure to complete AE/MAAE/AESI/SAE when information is available	9 (0.4)	0	9 (0.3)
30 minutes or immediate reaction post follow up not completed	20 (1.0)	8 (1.1)	28 (1.0)
Missing or not provided subject's diary card	129 (6.1)	45 (6.4)	174 (6.2)
Failure to capture AE/AESI/SAE/MAAE	4 (0.2)	0	4 (0.1)
Inexistent, missing or incomplete source data	8 (0.4)	1 (0.1)	9 (0.3)
Other	30 (1.4)	11 (1.6)	41 (1.5)
Study participants with at least one critical protocol deviation	1 (<0.1)	0	1 (<0.1)
History of any neurologic disorders, including any seizures and progressive neurologic disorders	1 (<0.1)	0	1 (<0.1)

n: number of subjects fulfilling the item listed
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.
Group 2: MENVEO® vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.

Efficacy results

Not applicable.

Safety results

Of the 2797 subjects enrolled and randomised, a total of 1799 subjects (85.7%) in Group 1 and 611 subjects (87.5%) in Group 2 completed the study.

Safety results were described for subjects in all study groups after vaccination at 2, 4, 6, and 12 months of age (Visit 1, Visit 2, Visit 3, and Visit 4, respectively).

Safety Summary After Any Dose (Overall SafAS)

Within 30 days of vaccination, 7 subjects (0.3%) in Group 1 were and 1 subject (0.1%) in Group 2 were discontinued from the study due to at least 1 AE. None of the adverse events of special interest (AESIs)/ medically attended adverse event (MAAEs) reported within 30 days or the serious adverse events (SAEs) and deaths reported during the study were considered related to vaccination.

Table 8: Safety overview after vaccine injection – Overall Safety Analysis Set for Any Dose

	Group 1 (N=2080)			Group 2 (N=697)		
Subjects experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Within 30 mins after any vaccine injections						
Immediate unsolicited AE	7/2080	0.3	(0.1 ; 0.7)	2/697	0.3	(0 ; 1.0)
Immediate unsolicited AR	3/2080	0.1	(0 ; 0.4)	1/697	0.1	(0 ; 0.8)
Solicited reaction from D0 to D7 within solicited period after any vaccine injections	1850/2021	91.5	(90.2 ; 92.7)	628/676	92.9	(90.7 ; 94.7)
Solicited injection site reaction	1715/2021	84.9	(83.2 ; 86.4)	572/676	84.6	(81.7 ; 87.3)
Solicited injection site after injection of MenACYW or MENVEO	1596/2021	79.0	(77.1 ; 80.7)	525/676	77.7	(74.3 ; 80.8)
Solicited injection site after injection of PENTACEL	1500/2017	74.4	(72.4 ; 76.3)	496/676	73.4	(69.9 ; 76.7)
Solicited injection site after injection of PREVNAR 13	1559/2018	77.3	(75.4 ; 79.1)	531/676	78.6	(75.3 ; 81.6)
Solicited injection site after injection of ENGERIX-B	1317/2013	65.4	(63.3 ; 67.5)	446/675	66.1	(62.4 ; 69.6)
Solicited injection site after injection of M-M-R II	873/1756	49.7	(47.4 ; 52.1)	302/588	51.4	(47.2 ; 55.5)
Solicited injection site after injection of VARIVAX	813/1758	46.2	(43.9 ; 48.6)	289/588	49.1	(45.0 ; 53.3)
Solicited systemic reaction	1759/2019	87.1	(85.6 ; 88.6)	596/676	88.2	(85.5 ; 90.5)
Within 30 days after any vaccine injections						
Unsolicited AE	1352/2080	65.0	(62.9 ; 67.1)	437/697	62.7	(59.0 ; 66.3)
Unsolicited AR	216/2080	10.4	(9.1 ; 11.8)	74/697	10.6	(8.4 ; 13.1)
Unsolicited non-serious AE	1347/2080	64.8	(62.7 ; 66.8)	437/697	62.7	(59.0 ; 66.3)
Unsolicited non-serious AR	216/2080	10.4	(9.1 ; 11.8)	74/697	10.6	(8.4 ; 13.1)
Unsolicited non-serious injection site AR	197/2080	9.5	(8.2 ; 10.8)	64/697	9.2	(7.1 ; 11.6)
Unsolicited non-serious injection site AR related to MenACYW or MENVEO	197/2080	9.5	(8.2 ; 10.8)	64/697	9.2	(7.1 ; 11.6)
Unsolicited non-serious injection site AR related to PENTACEL	160/2080	7.7	(6.6 ; 8.9)	40/697	5.7	(4.1 ; 7.7)
Unsolicited non-serious injection site AR related to PREVNAR 13	178/2080	8.6	(7.4 ; 9.8)	57/697	8.2	(6.3 ; 10.5)
Unsolicited non-serious injection site AR related to ENGERIX-B	83/2080	4.0	(3.2 ; 4.9)	24/697	3.4	(2.2 ; 5.1)
Unsolicited non-serious injection site AR related to M-M-R II	54/2080	2.6	(2.0 ; 3.4)	12/697	1.7	(0.9 ; 3.0)
Unsolicited non-serious injection site AR related to VARIVAX	70/2080	3.4	(2.6 ; 4.2)	15/697	2.2	(1.2 ; 3.5)
Unsolicited non-serious systemic AE	1244/2080	59.8	(57.7 ; 61.9)	407/697	58.4	(54.6 ; 62.1)
Unsolicited non-serious systemic AR	29/2080	1.4	(0.9 ; 2.0)	12/697	1.7	(0.9 ; 3.0)
AE leading to study discontinuation	7/2080	0.3	(0.1 ; 0.7)	1/697	0.1	(0 ; 0.8)
SAE	44/2080	2.1	(1.5 ; 2.8)	9/697	1.3	(0.6 ; 2.4)
Death	3/2080	0.1	(0 ; 0.4)	0/697	0	(0 ; 0.5)
AESI	5/2080	0.2	(0.1 ; 0.6)	0/697	0	(0 ; 0.5)
MAAE	1060/2080	51.0	(48.8 ; 53.1)	339/697	48.6	(44.9 ; 52.4)
During the study						
SAE	108/2080	5.2	(4.3 ; 6.2)	21/697	3.0	(1.9 ; 4.6)
Death	3/2080	0.1	(0 ; 0.4)	0/697	0	(0 ; 0.5)
AESI	19/2080	0.9	(0.6 ; 1.4)	1/697	0.1	(0 ; 0.8)
MAAE	1581/2080	76.0	(74.1 ; 77.8)	526/697	75.5	(72.1 ; 78.6)

n: number of subjects experiencing the endpoint listed in the first column. M: number of subjects with available data for the relevant endpoint.
N: number of subjects in overall safety analysis set for any dose. Percentages are based on M.
"Immediate unsolicited AE" is collected only for immediate unsolicited systemic AEs.
"Unsolicited AE" also includes immediate and serious unsolicited AEs. "Unsolicited non-serious AE" includes any unsolicited AE that is non-serious.
"MAAE" is medically-attended adverse event. "AESI" is adverse events of special interest.
AR: Reactions related to study vaccine (MenACYW/MENVEO); Unsolicited injection site reactions related to NIMP (routine vaccines) are reported separately
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.
Group 2: MENVEO® vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.

Table 9: Summary of solicited reactions within 7 days after vaccine injection – Overall Safety Analysis Set for Any Dose

	Group 1 (N=2080)			Group 2 (N=697)		
Subjects experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Solicited reaction	1850/2021	91.5	(90.2 ; 92.7)	628/676	92.9	(90.7 ; 94.7)
Grade 3 solicited reaction	510/2021	25.2	(23.4 ; 27.2)	162/676	24.0	(20.8 ; 27.4)
Solicited injection site reaction	1715/2021	84.9	(83.2 ; 86.4)	572/676	84.6	(81.7 ; 87.3)
Post-Injection MenACYW or MENVEO	1596/2021	79.0	(77.1 ; 80.7)	525/676	77.7	(74.3 ; 80.8)
Post-Injection PENTACEL	1500/2017	74.4	(72.4 ; 76.3)	496/676	73.4	(69.9 ; 76.7)
Post-Injection PREVNAR 13	1559/2018	77.3	(75.4 ; 79.1)	531/676	78.6	(75.3 ; 81.6)
Post-Injection ENGERIX-B	1317/2013	65.4	(63.3 ; 67.5)	446/675	66.1	(62.4 ; 69.6)
Post-Injection M-M-R II	873/1756	49.7	(47.4 ; 52.1)	302/588	51.4	(47.2 ; 55.5)
Post-Injection VARIVAX	813/1758	46.2	(43.9 ; 48.6)	289/588	49.1	(45.0 ; 53.3)
Grade 3 injection site reaction	259/2021	12.8	(11.4 ; 14.4)	76/676	11.2	(9.0 ; 13.9)
Post-Injection MenACYW or MENVEO	168/2021	8.3	(7.1 ; 9.6)	54/676	8.0	(6.1 ; 10.3)
Post-Injection PENTACEL	144/2017	7.1	(6.1 ; 8.4)	46/676	6.8	(5.0 ; 9.0)
Post-Injection PREVNAR 13	189/2018	9.4	(8.1 ; 10.7)	61/676	9.0	(7.0 ; 11.4)
Post-Injection ENGERIX-B	89/2013	4.4	(3.6 ; 5.4)	34/675	5.0	(3.5 ; 7.0)
Post-Injection M-M-R II	37/1756	2.1	(1.5 ; 2.9)	10/588	1.7	(0.8 ; 3.1)
Post-Injection VARIVAX	37/1758	2.1	(1.5 ; 2.9)	10/588	1.7	(0.8 ; 3.1)
Solicited systemic reaction	1759/2019	87.1	(85.6 ; 88.6)	596/676	88.2	(85.5 ; 90.5)
Grade 3 systemic reaction	379/2019	18.8	(17.1 ; 20.5)	128/676	18.9	(16.0 ; 22.1)

N: number of subjects in overall safety analysis set for any dose. n: number of subjects experiencing the endpoint listed in the first column.
M: number of subjects with available data for the relevant endpoint. Percentages are based on M.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.
Group 2: MENVEO® vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.

Safety Summary - After the first MenACYW conjugate vaccine dose at 2 months of age (SafAS1)

Within 30 days after vaccine injections at 2 months of age, 6 subjects (0.3%) in Group 1 and 1 subject (0.1%) in Group 2 were discontinued from the study due to at least 1 AE. In Group 1, 2 subjects who discontinued the study due to safety experienced AEs of pyrexia, crying, injection site pain, injection site rash, or irritability that were considered related to vaccination. In Group 2, the subject who discontinued the study due to safety experienced the AE of anaphylactic reaction that was considered related to vaccination.

Table 10: Safety overview after vaccine injection at 2 Months of Age – Safety Analysis Set 1

	Group 1 (N=2080)			Group 2 (N=697)		
Subjects experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Within 30 mins after any vaccine injections						
Immediate unsolicited AE	3/2080	0.1	(0 ; 0.4)	0/697	0	(0 ; 0.5)
Immediate unsolicited AR	1/2080	<0.1	(0 ; 0.3)	0/697	0	(0 ; 0.5)
Solicited reaction from D0 to D7 within solicited period after any vaccine injections	1653/2008	82.3	(80.6 ; 84.0)	553/674	82.0	(78.9 ; 84.9)
Solicited injection site reaction	1270/2008	63.2	(61.1 ; 65.4)	429/674	63.6	(59.9 ; 67.3)
Solicited injection site after injection of MenACYW or MENVEO	1093/2008	54.4	(52.2 ; 56.6)	372/674	55.2	(51.3 ; 59.0)
Solicited injection site after injection of PENTACEL	1063/2006	53.0	(50.8 ; 55.2)	371/673	55.1	(51.3 ; 58.9)
Solicited injection site after injection of PREVNAR 13	1049/2004	52.3	(50.1 ; 54.6)	356/674	52.8	(49.0 ; 56.6)
Solicited injection site after injection of ENGERIX-B	998/2005	49.8	(47.6 ; 52.0)	351/674	52.1	(48.2 ; 55.9)
Solicited systemic reaction	1510/2005	75.3	(73.4 ; 77.2)	501/674	74.3	(70.9 ; 77.6)
Within 30 days after any vaccine injections						
Unsolicited AE	589/2080	28.3	(26.4 ; 30.3)	187/697	26.8	(23.6 ; 30.3)
Unsolicited AR	85/2080	4.1	(3.3 ; 5.0)	23/697	3.3	(2.1 ; 4.9)
Unsolicited non-serious AE	580/2080	27.9	(26.0 ; 29.9)	187/697	26.8	(23.6 ; 30.3)
Unsolicited non-serious AR	85/2080	4.1	(3.3 ; 5.0)	23/697	3.3	(2.1 ; 4.9)
Unsolicited non-serious injection site AR	80/2080	3.8	(3.1 ; 4.8)	20/697	2.9	(1.8 ; 4.4)
Unsolicited non-serious injection site AR related to MenACYW or MENVEO	80/2080	3.8	(3.1 ; 4.8)	20/697	2.9	(1.8 ; 4.4)
Unsolicited non-serious injection site AR related to PENTACEL	81/2080	3.9	(3.1 ; 4.8)	21/697	3.0	(1.9 ; 4.6)
Unsolicited non-serious injection site AR related to PREVNAR 13	51/2080	2.5	(1.8 ; 3.2)	17/697	2.4	(1.4 ; 3.9)
Unsolicited non-serious injection site AR related to ENGERIX-B	58/2080	2.8	(2.1 ; 3.6)	18/697	2.6	(1.5 ; 4.1)
Unsolicited non-serious systemic AE	455/2080	21.9	(20.1 ; 23.7)	151/697	21.7	(18.7 ; 24.9)
Unsolicited non-serious systemic AR	6/2080	0.3	(0.1 ; 0.6)	3/697	0.4	(0.1 ; 1.3)
AE leading to study discontinuation	6/2080	0.3	(0.1 ; 0.6)	1/697	0.1	(0 ; 0.8)
SAE	23/2080	1.1	(0.7 ; 1.7)	4/697	0.6	(0.2 ; 1.5)
Death	2/2080	<0.1	(0 ; 0.3)	0/697	0	(0 ; 0.5)
AESI	2/2080	<0.1	(0 ; 0.3)	0/697	0	(0 ; 0.5)
MAAE	351/2080	16.9	(15.3 ; 18.6)	118/697	16.9	(14.2 ; 19.9)
During the study						
SAE	33/2080	1.6	(1.1 ; 2.2)	5/697	0.7	(0.2 ; 1.7)
Death	2/2080	<0.1	(0 ; 0.3)	0/697	0	(0 ; 0.5)
AESI	3/2080	0.1	(0 ; 0.4)	0/697	0	(0 ; 0.5)
MAAE	715/2080	34.4	(32.3 ; 36.5)	236/697	33.9	(30.3 ; 37.5)

n: number of subjects experiencing the endpoint listed in the first column. M: number of subjects with available data for the relevant endpoint.
N: number of subjects in safety analysis set for vaccination at 2 months of age. Percentages are based on M.
"Immediate unsolicited AE" is collected only for immediate unsolicited systemic AEs.
"Unsolicited AE" also includes immediate and serious unsolicited AEs. "Unsolicited non-serious AE" includes any unsolicited AE that is non-serious.
"MAAE" is medically-attended adverse event. "AESI" is adverse events of special interest.
AR: Reactions related to study vaccine (MenACYW/MENVEO); Unsolicited injection site reactions related to NIMP (routine vaccines) are reported separately.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.
Group 2: MENVEO® vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.

Table 10: Summary of solicited reactions within 7 days after vaccine injection at 2 Months of Age – Safety Analysis Set 1

Subjects experiencing at least one:	Group 1 (N=2080) n/M	%	(95% CI)	Group 2 (N=697) n/M	%	(95% CI)
Solicited reaction	1653/2008	82.3	(80.6 ; 84.0)	553/674	82.0	(78.9 ; 84.9)
Grade 3 solicited reaction	211/2008	10.5	(9.2 ; 11.9)	69/674	10.2	(8.1 ; 12.8)
Solicited injection site reaction	1270/2008	63.2	(61.1 ; 65.4)	429/674	63.6	(59.9 ; 67.3)
Post-Injection MenACYW or MENVEO	1093/2008	54.4	(52.2 ; 56.6)	372/674	55.2	(51.3 ; 59.0)
Post-Injection PENTACEL	1063/2006	53.0	(50.8 ; 55.2)	371/673	55.1	(51.3 ; 58.9)
Post-Injection PREVNAR 13	1049/2004	52.3	(50.1 ; 54.6)	356/674	52.8	(49.0 ; 56.6)
Post-Injection ENGERIX-B	998/2005	49.8	(47.6 ; 52.0)	351/674	52.1	(48.2 ; 55.9)
Grade 3 injection site reaction	106/2008	5.3	(4.3 ; 6.3)	33/674	4.9	(3.4 ; 6.8)
Post-Injection MenACYW or MENVEO	74/2008	3.7	(2.9 ; 4.6)	27/674	4.0	(2.7 ; 5.8)
Post-Injection PENTACEL	75/2006	3.7	(3.0 ; 4.7)	21/673	3.1	(1.9 ; 4.7)
Post-Injection PREVNAR 13	77/2004	3.8	(3.0 ; 4.8)	23/674	3.4	(2.2 ; 5.1)
Post-Injection ENGERIX-B	63/2005	3.1	(2.4 ; 4.0)	23/674	3.4	(2.2 ; 5.1)
Solicited systemic reaction	1510/2005	75.3	(73.4 ; 77.2)	501/674	74.3	(70.9 ; 77.6)
Grade 3 systemic reaction	139/2005	6.9	(5.9 ; 8.1)	48/674	7.1	(5.3 ; 9.3)

N: number of subjects in safety analysis set for vaccinations at 2 months of age.
n: number of subjects experiencing the endpoint listed in the first column
M: number of subjects with available data for the relevant endpoint
Percentages are based on M
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.
Group 2: MENVEO® vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.

Safety Summary - After the second MenACYW conjugate vaccine dose at 4 months of age (SafAS2)

Within 30 days after vaccine injections at 4 months of age, 1 subject (0.1%) in Group 1 was discontinued from the study due to at least 1 AE and no subjects in Group 2 were discontinued from the study. In this subject who discontinued the study, the AE of injection site erythema was considered related to vaccination.

Table 11: Safety overview after vaccine injection at 4 Months of Age – Safety Analysis Set 2

Subjects experiencing at least one:	Group 1 (N=2006) n/M	%	(95% CI)	Group 2 (N=663) n/M	%	(95% CI)
Within 30 mins after any vaccine injections						
Immediate unsolicited AE	2/2006	<0.1	(0 ; 0.4)	0/663	0	(0 ; 0.6)
Immediate unsolicited AR	0/2006	0	(0 ; 0.2)	0/663	0	(0 ; 0.6)
Solicited reaction from D0 to D7 within solicited period after any vaccine injections	1557/1928	80.8	(78.9 ; 82.5)	526/638	82.4	(79.3 ; 85.3)
Solicited injection site reaction	1232/1927	63.9	(61.7 ; 66.1)	410/638	64.3	(60.4 ; 68.0)
Solicited injection site after injection of MenACYW or MENVEO	1042/1927	54.1	(51.8 ; 56.3)	337/638	52.8	(48.9 ; 56.8)
Solicited injection site after injection of PENTACEL	1070/1927	55.5	(53.3 ; 57.8)	361/638	56.6	(52.6 ; 60.5)
Solicited injection site after injection of PREVNAR 13	1068/1925	55.5	(53.2 ; 57.7)	357/638	56.0	(52.0 ; 59.9)
Solicited systemic reaction	1378/1927	71.5	(69.4 ; 73.5)	475/638	74.5	(70.9 ; 77.8)
Within 30 days after any vaccine injections						
Unsolicited AE	649/2006	32.4	(30.3 ; 34.4)	193/663	29.1	(25.7 ; 32.7)
Unsolicited AR	55/2006	2.7	(2.1 ; 3.6)	22/663	3.3	(2.1 ; 5.0)
Unsolicited non-serious AE	647/2006	32.3	(30.2 ; 34.3)	193/663	29.1	(25.7 ; 32.7)
Unsolicited non-serious AR	55/2006	2.7	(2.1 ; 3.6)	22/663	3.3	(2.1 ; 5.0)
Unsolicited non-serious injection site AR	52/2006	2.6	(1.9 ; 3.4)	20/663	3.0	(1.9 ; 4.6)
Unsolicited non-serious injection site AR related to MenACYW or MENVEO	52/2006	2.6	(1.9 ; 3.4)	20/663	3.0	(1.9 ; 4.6)
Unsolicited non-serious injection site AR related to PENTACEL	51/2006	2.5	(1.9 ; 3.3)	16/663	2.4	(1.4 ; 3.9)
Unsolicited non-serious injection site AR related to PREVNAR 13	60/2006	3.0	(2.3 ; 3.8)	17/663	2.6	(1.5 ; 4.1)
Unsolicited non-serious systemic AE	573/2006	28.6	(26.6 ; 30.6)	169/663	25.5	(22.2 ; 29.0)
Unsolicited non-serious systemic AR	5/2006	0.2	(0.1 ; 0.6)	2/663	0.3	(0 ; 1.1)
AE leading to study discontinuation	1/2006	<0.1	(0 ; 0.3)	0/663	0	(0 ; 0.6)
SAE	4/2006	0.2	(0.1 ; 0.5)	0/663	0	(0 ; 0.6)
Death	0/2006	0	(0 ; 0.2)	0/663	0	(0 ; 0.6)
AESI	0/2006	0	(0 ; 0.2)	0/663	0	(0 ; 0.6)
MAAE	445/2006	22.2	(20.4 ; 24.1)	129/663	19.5	(16.5 ; 22.7)
During the study						
SAE	11/2006	0.5	(0.3 ; 1.0)	2/663	0.3	(0 ; 1.1)
Death	0/2006	0	(0 ; 0.2)	0/663	0	(0 ; 0.6)
AESI	0/2006	0	(0 ; 0.2)	0/663	0	(0 ; 0.6)
MAAE	811/2006	40.4	(38.3 ; 42.6)	256/663	38.6	(34.9 ; 42.4)

n: number of subjects experiencing the endpoint listed in the first column. M: number of subjects with available data for the relevant endpoint.
N: number of subjects in safety analysis set for vaccination at 4 months of age. Percentages are based on M.
"Immediate unsolicited AE" is collected only for immediate unsolicited systemic AEs.
"Unsolicited AE" also includes immediate and serious unsolicited AEs. "Unsolicited non-serious AE" includes any unsolicited AE that is non-serious.
"MAAE" is medically-attended adverse event. "AESI" is adverse events of special interest.
AR: Reactions related to study vaccine (MenACYW/MENVEO); Unsolicited injection site reactions related to NIMP (routine vaccines) are reported separately.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.
Group 2: MENVEO® vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.

Table 12: Summary of solicited reactions within 7 days after vaccine injections at 4 Months of Age – Safety Analysis Set 2

		Group 1 (N=2006)			Group 2 (N=663)	
Subjects experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Solicited reaction	1557/1928	80.8	(78.9 ; 82.5)	526/638	82.4	(79.3 ; 85.3)
Grade 3 solicited reaction	186/1928	9.6	(8.4 ; 11.1)	57/638	8.9	(6.8 ; 11.4)
Solicited injection site reaction	1232/1927	63.9	(61.7 ; 66.1)	410/638	64.3	(60.4 ; 68.0)
Post-Injection MenACYW or MENVEO	1042/1927	54.1	(51.8 ; 56.3)	337/638	52.8	(48.9 ; 56.8)
Post-Injection PENTACEL	1070/1927	55.5	(53.3 ; 57.8)	361/638	56.6	(52.6 ; 60.5)
Post-Injection PREVNAR 13	1068/1925	55.5	(53.2 ; 57.7)	357/638	56.0	(52.0 ; 59.9)
Grade 3 injection site reaction	82/1927	4.3	(3.4 ; 5.3)	19/638	3.0	(1.8 ; 4.6)
Post-Injection MenACYW or MENVEO	58/1927	3.0	(2.3 ; 3.9)	14/638	2.2	(1.2 ; 3.7)
Post-Injection PENTACEL	56/1927	2.9	(2.2 ; 3.8)	15/638	2.4	(1.3 ; 3.8)
Post-Injection PREVNAR 13	60/1925	3.1	(2.4 ; 4.0)	16/638	2.5	(1.4 ; 4.0)
Solicited systemic reaction	1378/1927	71.5	(69.4 ; 73.5)	475/638	74.5	(70.9 ; 77.8)
Grade 3 systemic reaction	145/1927	7.5	(6.4 ; 8.8)	49/638	7.7	(5.7 ; 10.0)

N: number of subjects in safety analysis set for vaccinations at 4 months of age.
n: number of subjects experiencing the endpoint listed in the first column.
M: number of subjects with available data for the relevant endpoint.
Percentages are based on M.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.
Group 2: MENVEO® vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.

Safety Summary - After the third MenACYW conjugate vaccine dose at 6 months of age (SafAS3)

Within 30 days after vaccine injections at 6 months of age, 1 subject (0.1%) in Group 1 was discontinued from the study due to at least 1 AE and no subjects in Group 2 were discontinued due to at least 1 AE. The AE of "unresponsive to stimuli" leading to the withdrawal of the subject in Group 1 from the study was considered as not related to vaccination by the Investigator.

Table 13: Safety overview after vaccine injection at 6 Months of Age – Safety Analysis Set 3

		Group 1 (N=1951)			Group 2 (N=648)	
Subjects experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Within 30 mins after any vaccine injections						
Immediate unsolicited AE	0/1951	0	(0 ; 0.2)	0/648	0	(0 ; 0.6)
Immediate unsolicited AR	0/1951	0	(0 ; 0.2)	0/648	0	(0 ; 0.6)
Solicited reaction from D0 to D7 within solicited period after any vaccine injections	1370/1797	76.2	(74.2 ; 78.2)	459/600	76.5	(72.9 ; 79.8)
Solicited injection site reaction	1135/1797	63.2	(60.9 ; 65.4)	373/600	62.2	(58.2 ; 66.1)
Solicited injection site after injection of MenACYW or MENVEO	974/1797	54.2	(51.9 ; 56.5)	310/599	51.8	(47.7 ; 55.8)
Solicited injection site after injection of PENTACEL	946/1794	52.7	(50.4 ; 55.1)	311/599	51.9	(47.8 ; 56.0)
Solicited injection site after injection of PREVNAR 13	920/1793	51.3	(49.0 ; 53.6)	307/599	51.3	(47.2 ; 55.3)
Solicited injection site after injection of ENGERIX-B	929/1791	51.9	(49.5 ; 54.2)	300/598	50.2	(46.1 ; 54.2)
Solicited systemic reaction	1178/1796	65.6	(63.3 ; 67.8)	389/600	64.8	(60.9 ; 68.7)
Within 30 days after any vaccine injections						
Unsolicited AE	547/1951	28.0	(26.1 ; 30.1)	186/648	28.7	(25.2 ; 32.4)
Unsolicited AR	48/1951	2.5	(1.8 ; 3.2)	16/648	2.5	(1.4 ; 4.0)
Unsolicited non-serious AE	544/1951	27.9	(25.9 ; 29.9)	186/648	28.7	(25.2 ; 32.4)
Unsolicited non-serious AR	48/1951	2.5	(1.8 ; 3.2)	16/648	2.5	(1.4 ; 4.0)
Unsolicited non-serious injection site AR	45/1951	2.3	(1.7 ; 3.1)	15/648	2.3	(1.3 ; 3.8)
Unsolicited non-serious injection site AR related to MenACYW or MENVEO	45/1951	2.3	(1.7 ; 3.1)	15/648	2.3	(1.3 ; 3.8)
Unsolicited non-serious injection site AR related to PENTACEL	48/1951	2.5	(1.8 ; 3.2)	13/648	2.0	(1.1 ; 3.4)
Unsolicited non-serious injection site AR related to PREVNAR 13	45/1951	2.3	(1.7 ; 3.1)	12/648	1.9	(1.0 ; 3.2)
Unsolicited non-serious injection site AR related to ENGERIX-B	35/1951	1.8	(1.3 ; 2.5)	7/648	1.1	(0.4 ; 2.2)
Unsolicited non-serious systemic AE	475/1951	24.3	(22.5 ; 26.3)	164/648	25.3	(22.0 ; 28.8)
Unsolicited non-serious systemic AR	4/1951	0.2	(0.1 ; 0.5)	1/648	0.2	(0 ; 0.9)
AE leading to study discontinuation	1/1951	<0.1	(0 ; 0.3)	0/648	0	(0 ; 0.6)
SAE	9/1951	0.5	(0.2 ; 0.9)	1/648	0.2	(0 ; 0.9)

Death	1/1951	<0.1	(0 ; 0.3)	0/648	0	(0 ; 0.6)
AESI	1/1951	<0.1	(0 ; 0.3)	0/648	0	(0 ; 0.6)
MAAE	392/1951	20.1	(18.3 ; 21.9)	134/648	20.7	(17.6 ; 24.0)
During the study						
SAE	35/1951	1.8	(1.3 ; 2.5)	4/648	0.6	(0.2 ; 1.6)
Death	1/1951	<0.1	(0 ; 0.3)	0/648	0	(0 ; 0.6)
AESI	10/1951	0.5	(0.2 ; 0.9)	1/648	0.2	(0 ; 0.9)
MAAE	1199/1951	61.5	(59.3 ; 63.6)	398/648	61.4	(57.5 ; 65.2)

n: number of subjects experiencing the endpoint listed in the first column. M: number of subjects with available data for the relevant endpoint.
N: number of subjects in safety analysis set for vaccination at 6 months of age. Percentages are based on M.
"Immediate unsolicited AE" is collected only for immediate unsolicited systemic AEs.
"Unsolicited AE" also includes immediate and serious unsolicited AEs. "Unsolicited non-serious AE" includes any unsolicited AE that is non-serious.
"MAAE" is medically-attended adverse event. "AESI" is adverse events of special interest.
AR: Reactions related to study vaccine (MenACYW/MENVEO); Unsolicited injection site reactions related to NIMP (routine vaccines) are reported separately.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.
Group 2: MENVEO® vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.

Table 14: Summary of solicited reactions within 7 days after vaccine injections at 6 Months of Age – Safety Analysis Set 3

	Group 1 (N=1951)			Group 2 (N=648)		
Subjects experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Solicited reaction	1370/1797	76.2	(74.2 ; 78.2)	459/600	76.5	(72.9 ; 79.8)
Grade 3 solicited reaction	125/1797	7.0	(5.8 ; 8.2)	42/600	7.0	(5.1 ; 9.3)
Solicited injection site reaction	1135/1797	63.2	(60.9 ; 65.4)	373/600	62.2	(58.2 ; 66.1)
Post-Injection MenACYW or MENVEO	974/1797	54.2	(51.9 ; 56.5)	310/599	51.8	(47.7 ; 55.8)
Post-Injection PENTACEL	946/1794	52.7	(50.4 ; 55.1)	311/599	51.9	(47.8 ; 56.0)
Post-Injection PREVNAR 13	920/1793	51.3	(49.0 ; 53.6)	307/599	51.3	(47.2 ; 55.3)
Post-Injection ENGERIX-B	929/1791	51.9	(49.5 ; 54.2)	300/598	50.2	(46.1 ; 54.2)
Grade 3 injection site reaction	61/1797	3.4	(2.6 ; 4.3)	18/600	3.0	(1.8 ; 4.7)
Post-Injection MenACYW or MENVEO	38/1797	2.1	(1.5 ; 2.9)	12/599	2.0	(1.0 ; 3.5)
Post-Injection PENTACEL	42/1794	2.3	(1.7 ; 3.2)	14/599	2.3	(1.3 ; 3.9)
Post-Injection PREVNAR 13	46/1793	2.6	(1.9 ; 3.4)	16/599	2.7	(1.5 ; 4.3)
Post-Injection ENGERIX-B	36/1791	2.0	(1.4 ; 2.8)	13/598	2.2	(1.2 ; 3.7)
Solicited systemic reaction	1178/1796	65.6	(63.3 ; 67.8)	389/600	64.8	(60.9 ; 68.7)
Grade 3 systemic reaction	95/1796	5.3	(4.3 ; 6.4)	31/600	5.2	(3.5 ; 7.3)

N: number of subjects in safety analysis set for vaccinations at 6 months of age.
n: number of subjects experiencing the endpoint listed in the first column.
M: number of subjects with available data for the relevant endpoint.
Percentages are based on M.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.
Group 2: MENVEO® vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.

Safety Summary - After the fourth MenACYW conjugate vaccine dose at 12 months of age (SafAS4)

Within 30 days after vaccine injections at 12 months of age, no subjects in either Group 1 or Group 2 discontinued the study due to at least 1 AE.

Table 15: Safety overview after vaccine injection at 12 Months of Age – Safety Analysis Set 4

	Group 1 (N=1838)			Group 2 (N=623)		
Subjects experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Within 30 mins after any vaccine injections						
Immediate unsolicited AE	3/1838	0.2	(0 ; 0.5)	2/623	0.3	(0 ; 1.2)
Immediate unsolicited AR	2/1838	0.1	(0 ; 0.4)	1/623	0.2	(0 ; 0.9)
Solicited reaction from D0 to D7 within solicited period after any vaccine injections	1342/1769	75.9	(73.8 ; 77.8)	458/593	77.2	(73.6 ; 80.6)
Solicited injection site reaction	1133/1768	64.1	(61.8 ; 66.3)	382/592	64.5	(60.5 ; 68.4)
Solicited injection site after injection of MenACYW or MENVEO	948/1767	53.7	(51.3 ; 56.0)	326/592	55.1	(51.0 ; 59.1)
Solicited injection site after injection of PREVNAR 13	950/1761	53.9	(51.6 ; 56.3)	323/589	54.8	(50.7 ; 58.9)
Solicited injection site after injection of M-M-R II	874/1757	49.7	(47.4 ; 52.1)	301/587	51.3	(47.2 ; 55.4)
Solicited injection site after injection of VARIVAX	814/1759	46.3	(43.9 ; 48.6)	288/587	49.1	(44.9 ; 53.2)
Solicited systemic reaction	1160/1767	65.6	(63.4 ; 67.9)	381/593	64.2	(60.2 ; 68.1)
Within 30 days after any vaccine injections						
Unsolicited AE	713/1838	38.8	(36.6 ; 41.1)	214/623	34.3	(30.6 ; 38.2)
Unsolicited AR	87/1838	4.7	(3.8 ; 5.8)	30/623	4.8	(3.3 ; 6.8)
Unsolicited non-serious AE	712/1838	38.7	(36.5 ; 41.0)	212/623	34.0	(30.3 ; 37.9)
Unsolicited non-serious AR	87/1838	4.7	(3.8 ; 5.8)	30/623	4.8	(3.3 ; 6.8)
Unsolicited non-serious injection site AR	71/1838	3.9	(3.0 ; 4.8)	23/623	3.7	(2.4 ; 5.5)
Unsolicited non-serious injection site AR related to MenACYW or MENVEO	71/1838	3.9	(3.0 ; 4.8)	23/623	3.7	(2.4 ; 5.5)
Unsolicited non-serious injection site AR related to PREVNAR 13	59/1838	3.2	(2.5 ; 4.1)	19/623	3.0	(1.8 ; 4.7)
Unsolicited non-serious injection site AR related to M-M-R II	54/1838	2.9	(2.2 ; 3.8)	12/623	1.9	(1.0 ; 3.3)
Unsolicited non-serious injection site AR related to VARIVAX	70/1838	3.8	(3.0 ; 4.8)	15/623	2.4	(1.4 ; 3.9)
Unsolicited non-serious systemic AE	621/1838	33.8	(31.6 ; 36.0)	191/623	30.7	(27.1 ; 34.4)
Unsolicited non-serious systemic AR	16/1838	0.9	(0.5 ; 1.4)	7/623	1.1	(0.5 ; 2.3)
AE leading to study discontinuation	0/1838	0	(0 ; 0.2)	0/623	0	(0 ; 0.6)
SAE	9/1838	0.5	(0.2 ; 0.9)	4/623	0.6	(0.2 ; 1.6)
Death	0/1838	0	(0 ; 0.2)	0/623	0	(0 ; 0.6)

AESI	3/1838	0.2	(0 ; 0.5)	0/623	0	(0 ; 0.6)
MAAE	447/1838	24.3	(22.4 ; 26.3)	129/623	20.7	(17.6 ; 24.1)
During the study						
SAE	33/1838	1.8	(1.2 ; 2.5)	12/623	1.9	(1.0 ; 3.3)
Death	0/1838	0	(0 ; 0.2)	0/623	0	(0 ; 0.6)
AESI	8/1838	0.4	(0.2 ; 0.9)	1/623	0.2	(0 ; 0.9)
MAAE	894/1838	48.6	(46.3 ; 51.0)	272/623	43.7	(39.7 ; 47.7)

n: number of subjects experiencing the endpoint listed in the first column. M: number of subjects with available data for the relevant endpoint.
N: number of subjects in safety analysis set for vaccination at 12 months of age. Percentages are based on M.
"Immediate unsolicited AE" is collected only for immediate unsolicited systemic AEs.
"Unsolicited AE" also includes immediate and serious unsolicited AEs. "Unsolicited non-serious AE" includes any unsolicited AE that is non-serious.
"MAAE" is medically-attended adverse event. "AESI" is adverse events of special interest.
AR: Reactions related to study vaccine (MenACYW/MENVEO); Unsolicited injection site reactions related to NIMP (routine vaccines) are reported separately.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.
Group 2: MENVEO® vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.

Table 16: Summary of solicited reactions within 7 days after vaccine injections at 12 Months of Age – Safety Analysis Set 4

	Group 1 (N=1838)			Group 2 (N=623)		
Subjects experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Solicited reaction	1342/1769	75.9	(73.8 ; 77.8)	458/593	77.2	(73.6 ; 80.6)
Grade 3 solicited reaction	175/1769	9.9	(8.5 ; 11.4)	50/593	8.4	(6.3 ; 11.0)
Solicited injection site reaction	1133/1768	64.1	(61.8 ; 66.3)	382/592	64.5	(60.5 ; 68.4)
Post-Injection MenACYW or MENVEO	948/1767	53.7	(51.3 ; 56.0)	326/592	55.1	(51.0 ; 59.1)
Post-Injection PREVNAR 13	950/1761	53.9	(51.6 ; 56.3)	323/589	54.8	(50.7 ; 58.9)
Post-Injection M-M-R II	874/1757	49.7	(47.4 ; 52.1)	301/587	51.3	(47.2 ; 55.4)
Post-Injection VARIVAX	814/1759	46.3	(43.9 ; 48.6)	288/587	49.1	(44.9 ; 53.2)
Grade 3 injection site reaction	90/1768	5.1	(4.1 ; 6.2)	21/592	3.5	(2.2 ; 5.4)
Post-Injection MenACYW or MENVEO	45/1767	2.5	(1.9 ; 3.4)	11/592	1.9	(0.9 ; 3.3)
Post-Injection PREVNAR 13	58/1761	3.3	(2.5 ; 4.2)	15/589	2.5	(1.4 ; 4.2)
Post-Injection M-M-R II	37/1757	2.1	(1.5 ; 2.9)	10/587	1.7	(0.8 ; 3.1)
Post-Injection VARIVAX	37/1759	2.1	(1.5 ; 2.9)	10/587	1.7	(0.8 ; 3.1)
Solicited systemic reaction	1160/1767	65.6	(63.4 ; 67.9)	381/593	64.2	(60.2 ; 68.1)
Grade 3 systemic reaction	125/1767	7.1	(5.9 ; 8.4)	34/593	5.7	(4.0 ; 7.9)

N: number of subjects in safety analysis set for vaccinations at 12 months of age.
n: number of subjects experiencing the endpoint listed in the first column.
M: number of subjects with available data for the relevant endpoint.
Percentages are based on M.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.
Group 2: MENVEO® vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.

Safety Summary - Subjects who received the entire 4-Dose MenACYW conjugate vaccine Vaccination (SafAS5)

Table 17: Safety overview after vaccine injection – Safety Analysis Set for all 4-Dose Vaccination

	Group 1 (N=1836)			Group 2 (N=622)		
Subjects experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Within 30 mins after any vaccine injections						
Immediate unsolicited AE	6/1836	0.3	(0.1 ; 0.7)	2/622	0.3	(0 ; 1.2)
Immediate unsolicited AR	2/1836	0.1	(0 ; 0.4)	1/622	0.2	(0 ; 0.9)
Solicited reaction from D0 to D7 within solicited period after any vaccine injections	1705/1833	93.0	(91.8 ; 94.1)	585/621	94.2	(92.1 ; 95.9)
Solicited injection site reaction	1597/1833	87.1	(85.5 ; 88.6)	535/621	86.2	(83.2 ; 88.8)
Solicited injection site after injection of MenACYW or MENVEO	1490/1833	81.3	(79.4 ; 83.0)	491/621	79.1	(75.7 ; 82.2)
Solicited injection site after injection of PENTACEL	1404/1830	76.7	(74.7 ; 78.6)	464/621	74.7	(71.1 ; 78.1)
Solicited injection site after injection of PREVNAR 13	1465/1832	80.0	(78.1 ; 81.8)	498/621	80.2	(76.8 ; 83.3)
Solicited injection site after injection of ENGERIX-B	1239/1829	67.7	(65.5 ; 69.9)	414/620	66.8	(62.9 ; 70.5)
Solicited injection site after injection of M-M-R II	873/1756	49.7	(47.4 ; 52.1)	300/586	51.2	(47.1 ; 55.3)
Solicited injection site after injection of VARIVAX	813/1758	46.2	(43.9 ; 48.6)	287/586	49.0	(44.9 ; 53.1)
Solicited systemic reaction	1635/1832	89.2	(87.7 ; 90.6)	558/621	89.9	(87.2 ; 92.1)
Within 30 days after any vaccine injections						
Unsolicited AE	1271/1836	69.2	(67.1 ; 71.3)	418/622	67.2	(63.4 ; 70.9)
Unsolicited AR	208/1836	11.3	(9.9 ; 12.9)	72/622	11.6	(9.2 ; 14.4)
Unsolicited non-serious AE	1269/1836	69.1	(66.9 ; 71.2)	418/622	67.2	(63.4 ; 70.9)
Unsolicited non-serious AR	208/1836	11.3	(9.9 ; 12.9)	72/622	11.6	(9.2 ; 14.4)
Unsolicited non-serious injection site AR	190/1836	10.3	(9.0 ; 11.8)	63/622	10.1	(7.9 ; 12.8)
Unsolicited non-serious injection site AR related to MenACYW or MENVEO	190/1836	10.3	(9.0 ; 11.8)	63/622	10.1	(7.9 ; 12.8)
Unsolicited non-serious injection site AR related to PENTACEL	151/1836	8.2	(7.0 ; 9.6)	38/622	6.1	(4.4 ; 8.3)
Unsolicited non-serious injection site AR related to PREVNAR 13	173/1836	9.4	(8.1 ; 10.9)	55/622	8.8	(6.7 ; 11.4)
Unsolicited non-serious injection site AR related to ENGERIX-B	80/1836	4.4	(3.5 ; 5.4)	23/622	3.7	(2.4 ; 5.5)
Unsolicited non-serious injection site AR related to M-M-R II	54/1836	2.9	(2.2 ; 3.8)	12/622	1.9	(1.0 ; 3.3)
Unsolicited non-serious injection site AR related to VARIVAX	70/1836	3.8	(3.0 ; 4.8)	15/622	2.4	(1.4 ; 3.9)

Unsolicited non-serious systemic AE	1174/1836	63.9	(61.7 ; 66.1)	389/622	62.5	(58.6 ; 66.4)
Unsolicited non-serious systemic AR	28/1836	1.5	(1.0 ; 2.2)	11/622	1.8	(0.9 ; 3.1)
AE leading to study discontinuation	0/1836	0	(0 ; 0.2)	0/622	0	(0 ; 0.6)
SAE	36/1836	2.0	(1.4 ; 2.7)	9/622	1.4	(0.7 ; 2.7)
Death	0/1836	0	(0 ; 0.2)	0/622	0	(0 ; 0.6)
AESI	4/1836	0.2	(0.1 ; 0.6)	0/622	0	(0 ; 0.6)
MAAE	1002/1836	54.6	(52.3 ; 56.9)	322/622	51.8	(47.8 ; 55.8)
During the study						
SAE	93/1836	5.1	(4.1 ; 6.2)	21/622	3.4	(2.1 ; 5.1)
Death	0/1836	0	(0 ; 0.2)	0/622	0	(0 ; 0.6)
AESI	17/1836	0.9	(0.5 ; 1.5)	1/622	0.2	(0 ; 0.9)
MAAE	1488/1836	81.0	(79.2 ; 82.8)	498/622	80.1	(76.7 ; 83.1)

n: number of subjects experiencing the endpoint listed in the first column. M: number of subjects with available data for the relevant endpoint.
N: number of subjects who have received all 4-dose vaccinations in a series of either all MenACYW or all MENVEO®. Percentages are based on M.
"Immediate unsolicited AE" is collected only for immediate unsolicited systemic AEs.
"Unsolicited AE" also includes immediate and serious unsolicited AEs. "Unsolicited non-serious AE" includes any unsolicited AE that is non-serious.
"MAAE" is medically-attended adverse event. "AESI" is adverse events of special interest.
AR: Reactions related to study vaccine (MenACYW/MENVEO); Unsolicited injection site reactions related to NIMP (routine vaccines) are reported separately.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.
Group 2: MENVEO® vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.

Table 18: Summary of solicited reactions within 7 days after vaccine injection – Safety Analysis Set for all 4-Dose Vaccination

	Group 1 (N=1836)			Group 2 (N=622)		
Subjects experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Solicited reaction	1705/1833	93.0	(91.8 ; 94.1)	585/621	94.2	(92.1 ; 95.9)
Grade 3 solicited reaction	482/1833	26.3	(24.3 ; 28.4)	147/621	23.7	(20.4 ; 27.2)
Solicited injection site reaction	1597/1833	87.1	(85.5 ; 88.6)	535/621	86.2	(83.2 ; 88.8)
Post-Injection MenACYW or MENVEO	1490/1833	81.3	(79.4 ; 83.0)	491/621	79.1	(75.7 ; 82.2)
Post-Injection PENTACEL	1404/1830	76.7	(74.7 ; 78.6)	464/621	74.7	(71.1 ; 78.1)
Post-Injection PREVNAR 13	1465/1832	80.0	(78.1 ; 81.8)	498/621	80.2	(76.8 ; 83.3)
Post-Injection ENGERIX-B	1239/1829	67.7	(65.5 ; 69.9)	414/620	66.8	(62.9 ; 70.5)
Post-Injection M-M-R II	873/1756	49.7	(47.4 ; 52.1)	300/586	51.2	(47.1 ; 55.3)
Post-Injection VARIVAX	813/1758	46.2	(43.9 ; 48.6)	287/586	49.0	(44.9 ; 53.1)
Grade 3 injection site reaction	245/1833	13.4	(11.8 ; 15.0)	70/621	11.3	(8.9 ; 14.0)
Post-Injection MenACYW or MENVEO	155/1833	8.5	(7.2 ; 9.8)	50/621	8.1	(6.0 ; 10.5)
Post-Injection PENTACEL	131/1830	7.2	(6.0 ; 8.4)	44/621	7.1	(5.2 ; 9.4)
Post-Injection PREVNAR 13	176/1832	9.6	(8.3 ; 11.0)	59/621	9.5	(7.3 ; 12.1)
Post-Injection ENGERIX-B	81/1829	4.4	(3.5 ; 5.5)	31/620	5.0	(3.4 ; 7.0)
Post-Injection M-M-R II	37/1756	2.1	(1.5 ; 2.9)	10/586	1.7	(0.8 ; 3.1)
Post-Injection VARIVAX	37/1758	2.1	(1.5 ; 2.9)	10/586	1.7	(0.8 ; 3.1)
Solicited systemic reaction	1635/1832	89.2	(87.7 ; 90.6)	558/621	89.9	(87.2 ; 92.1)
Grade 3 systemic reaction	359/1832	19.6	(17.8 ; 21.5)	116/621	18.7	(15.7 ; 22.0)

N: number of subjects in safety analysis set for all 4-dose vaccinations.
n: number of subjects experiencing the endpoint listed in the first column.
M: number of subjects with available data for the relevant endpoint.
Percentages are based on M.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.
Group 2: MENVEO® vaccine and routine pediatric vaccines administered at 2, 4, 6, and 12 months of age.

2.3.3. Discussion on clinical aspects

MET41 was a phase III, modified double-blind, randomised, parallel-group, active-controlled, multi-centre study to describe the safety of MenACYW conjugate vaccine and the comparator vaccine MENVEO when administered concomitantly with routine paediatric vaccines given to healthy infants and toddlers (Group 1: MenACYW conjugate vaccine + routine paediatric vaccines; Group 2: MENVEO + routine paediatric vaccines). The meningococcal vaccines were administered in 4 doses at 2, 4, 6, and 12 months of age. The study report of this paediatric study was submitted within 6 months after study completion as required with Article 46 of Regulation (EC) No. 1901/2006, as amended. MENVEO is currently approved in the EU from the age of 2 years (single dose). At submission of the planned type II variation, the MAH should discuss the use of MENVEO as comparator vaccine. Furthermore, at the time of variation submission the MAH should justify a possible extrapolation of the concomitant vaccines and schedules used to the European situation (available vaccines and recommended vaccination schedules in the EU).

Solicited AE information for both solicited injection site reactions and solicited systemic reactions was collected from D0 up to D07 after each vaccination. Immediate unsolicited systemic adverse events were collected within 30 minutes after each vaccination. Unsolicited AE information was collected from D0 up to D30 after each vaccination. SAE information (including AESIs and MAAEs) was collected throughout the study from Visit 1 (day of first vaccination) until the end of the 6-month follow up period after the last vaccination. These measurements are considered appropriate.

A total of 2797 subjects were randomised: 2099 subjects to Group 1 and 698 to Group 2. Overall, a total of 2777 subjects received at least one dose of study vaccine, 2080 subjects in Group 1 and 697 in Group 2. Hence, the 3:1 randomisation strategy yielded a rather small sample size to detect the less frequent AEs for the comparator vaccine. Overall, groups were comparable regarding the baseline demographics (sex, age, and ethnicity). For instance, the mean age was 64.7 days (±6.63) in Group 1 and 64.9 days (±6.77) in Group 2. There were slightly more males than females in both vaccination groups (52.5% in Group 1 and 51.9% in Group 2), which is acceptable.

Concomitant vaccinations were similarly distributed between groups. For instance, at visit 4, a total of 2452 subjects (87.7%) received PREVNAR 13: 1832 subjects (87.3%) in Group 1 and 620 subjects (88.8%) in Group 2. A total of 2448 subjects (87.5%) received VARIVAX: 1830 subjects (87.2%) in Group 1 and 618 subjects (88.5%) in Group 2. A total of 2445 subjects (87.4%) received M-M-R II: 1827 subjects (87.0%) in Group 1 and 618 subjects (88.5%) in Group 2. Therefore, the exposure to different infant vaccines was comparable between the MenACYW and MENVEO groups.

The safety data was presented descriptively (no efficacy or immunogenicity data was provided with study MET41).

In the SafAS Overall Population, 91.5% and 92.9% of subjects were experiencing at least one solicited reaction from D0 to D7 after vaccination with MenACYW (group 1) and MENVEO (group 2), respectively. Injection site reactions (such as injection site pain or erythema) were observed in 84.9% (group 1) and 84.6% (group 2) of subjects, respectively. Injection site reactions following the different concomitant vaccines were also comparable between groups at any dose (e.g., solicited injection site reaction after injection of M-M-R II: 49.7% of subjects (group 1) and 51.4% of subjects (group 2). Solicited systemic reactions (such as drowsiness and fever) were observed in 87.1% (group 1) and 88.2% (group 2) of subjects. Within 30 days after any dose, unsolicited AEs occurred in 65.0% and 62.7% of subjects in group 1 and group 2, respectively. At least 1 unsolicited non-serious AR was assessed as related to vaccination in 10.4% and 10.6% of subjects in group 1 and group 2, respectively. Most unsolicited ARs started during the time period D0-D3 and resolved after 1-3 days and 4-7 days in group 1 and group 2, respectively. In summary, the incidence and nature of AEs were comparable between MenACYW and MENVEO groups after vaccination with either meningococcal vaccine. Likewise, injection site reactions after vaccination with the concomitant paediatric vaccines were highly similar between groups.

Importantly, none of the AESIs, MAAEs, SAEs and deaths reported during the study (SafAS) were considered related to vaccination. Also, the majority of SAEs recovered or resolved during the study (120 of 133 events in group 1 and 25 of 26 events in group 2). This is somewhat reassuring since a numerically higher incidence for these safety parameters was observed during the study in the MenACYW group compared to the MENVEO group (MenACYW vs MENVEO: AESIs: 0.9% vs 0.1% of subjects; MAAEs: 76% vs. 75.5%; SAEs: 5.2% vs 3.0%; deaths: 0.1% vs 0.0%).

Three deaths were reported during the study (all in the MenACYW group). One subject (a 12-week-old male; unknown ethnicity) deceased following a non-accidental injury of the head 30 days after injection of the first dose of MenACYW conjugate vaccine with routine paediatric vaccines. The second subject (12-week-old Black male) had sudden unexplained death in infancy, 24 days after first dose injection with investigational vaccine administered concomitantly with first doses of DTaP-IPV-Hib, hepatitis B vaccine, pneumococcal 13-valent conjugate vaccine, and rotavirus vaccine. The investigator defined the primary cause of death as sudden unexplained infant death and the secondary cause of death as pulmonary oedema. The third subject (06-month-old Black female) had medical history of neonatal hypoglycaemia. The participant was found unresponsive in bed by parent, 4 days after third dose injection of investigational vaccine administered concomitantly with second dose of hepatitis B vaccine, and third doses of DTaP-IPV-Hib, pneumococcal 13-valent conjugate vaccine, and rotavirus vaccine. A health care provider was not contacted for the event. The primary cause of death was unknown, and the secondary cause of death was not reported. Thus, the primary cause for 2 of 3 deaths in subjects <12 months of age in the MenACYW group (both black individuals) remain obscure.

Besides reported fatal events, the higher rate in SAEs during the study is also reflected in life threatening events (0.3% vs. 0.1% of subjects), events requiring hospitalization (4.6% vs. 2.9% of subjects) and other medically important events (0.7% vs. 0.1% of subjects). Serious system organ class (SOC) General disorders and administration site conditions were reported only in group 1, but the incidence rate is low (4 vs. 0 events in group 1 and 2, respectively). Similarly, serious events in the SOC Injury poisoning and procedural complications were reported in 0.5% vs. 0% of subjects in group 1 and group 2, respectively. However, no specific preferred term (PT) was identified as risk and no PT that shows reasonable possibility to be in causal relation to vaccination. Serious lower respiratory tract infections in the SOC Infections and infestations (i.e. PTs Respiratory syncytial virus infection, Bronchiolitis, Respiratory syncytial virus bronchiolitis in SOC Infections and infestations) were reported by 1.2% of subjects in group 1, but only 0.3% of subjects in group 2. However, no difference is seen for the SOC Respiratory, thoracic, and mediastinal disorders (0.3% of subjects in either group). Whether serious respiratory tract infections are indeed associated to the vaccination with MenQuadfi is not clear, but should be discussed in more detail once licensure for subjects <12 months is requested.

A serious event in the SOC Nervous System Disorders was reported by 1.2% and 0.1% of subjects in group 1 and group 2, respectively. Of note, the majority of events was related to seizures/convulsions (i.e. PTs Febrile convulsion, Seizure, Epilepsy, Seizure like phenomena). Thus, it can be expected that a bit less than every 100th subject <12months will have a serious seizure/convulsion during the vaccination schedule (i.e. 4 doses) with MenQuadfi, whereas a factor 10 less subjects will be affected by these events during the vaccination schedule with Menveo. In line with this observation, all AESIs during the study (22 events in 19 subjects in group 1 vs. 2 events in 1 subject in group 2) were within these 4 PTs related to seizures/convulsions (i.e. PTs Febrile convulsion, Seizure, Epilepsy, Seizure like phenomena). Considering a possible relation to study treatment, 2 serious events (one PT Febrile convulsion and Seizure each) were reported within 7 days and 6 serious events (3 Febrile convulsion, 2 Seizure and 1 Seizure like phenomenon) within 30 days after vaccination in group 1 (none in group 2; all of these events were also rated as AESI). Thus, serious AEs in the SOC Nervous System Disorders and especially PTs with relation to seizures/convulsions should be discussed in detail once all data from the clinical developmental program in subjects <12months become available.

In addition to the SafAS Overall Population, the MAH also provided summaries after the first MenACYW conjugate vaccine dose at 2 months of age (SafAS1); after the second MenACYW conjugate vaccine dose at 4 months of age (SafAS2); after the third MenACYW conjugate vaccine dose at 6 months of age (SafAS3); after the fourth MenACYW conjugate vaccine dose at 12 months of age (SafAS4) and for subjects who received the entire 4-Dose MenACYW conjugate vaccine Vaccination (SafAS5). The different safety sets mirrored results obtained with the Safety Analysis Set (SafAS) Overall Population. Hence, no specific significant safety risk for a certain age group within study MET41 or after one specific dose was observed.

Only very few subjects discontinued participation in the study due to safety experienced AEs in the different age groups (mostly injections site reactions; up to 0,3% in the MenACYW group, at 2 months of age). Slightly more subjects discontinued due to AEs in the MenACYW group compared to the MENVEO group (11 [0.5%] vs 1 [0.1%] subjects). Overall, a total of 1799 subjects (85.7%) in Group 1 and 611 subjects (87.5%) in Group 2 completed the study, indicating a high and comparable vaccination acceptance for MenACYW and MENVEO vaccines.

Protocol Deviations were overall comparable between groups (group 1 25 subjects [1.2%] vs group 2 11 subjects [1.6%]) and do not indicate major irregularities in study conduct.

3. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

The fact that AEs were erroneously reported raises concerns on the integrity of study MET41 and raises the question about the correct reporting of AEs for other studies included in the planned variation. The Applicant is asked to perform a root-cause analysis and to outline measures to identify such issues in submitted and ongoing MenQuadfi studies as well as to prevent such errors in future submissions (OC).

The timetable is a 30-day response timetable with clock stop.

MAH responses to Request for supplementary information

Question:

The MAH is asked to provide an updated documentation with corrected errors and a clear communication of all applied changes. This should include a separate document that depicts all changes applied to tables, figures and text (i.e. previous erroneous and the respective amended version) and with reference in what part of the dossier and in which document the change was applied as well as all documents of the initial submission updated with the corrected information in the same format and manner as for the initial submission.

MAH response:

List of Changes from Critical Expert Overview Version 1.0 Dated 18 September 2023 to Version 2.0 Dated 18 December 2023

Note: In the Summary of Changes column in the table below, bold and underlined text is for text added and strikethrough text is for text deleted as part of this critical expert overview (CEO) addendum.

Section Number / Heading	Summary of Changes	Rationale for Change
CEO Summary of Changes	**Due to a programming discrepancy that had occurred during MET41 study statistical analysis, minor errors in the safety results were noted and have been corrected in the clinical study report (CSR) and this critical expert overview (CEO).** • **Unsolicited AEs with missing or partial missing dates that were previously not categorized as "occurred within 30 days" are now considered as "occurred within 30 days" and were added to the safety statistical analysis of "Unsolicited AE within 30 days after vaccination". This has increased the number of unsolicited non-serious AEs reported in the safety tables and now present the results in a more conservative way. All these AEs were non-serious and non-related to study products.** • **The denominator (M) of the safety tables describing "All and related AEs leading to study discontinuation, by SOC and PT" were wrongly computed and was updated using the definition "M: number of subjects in the safety analysis set". Numerators remain the same as the Version 1.0 of the CEO.** **These changes resulted in updates to relevant safety tables and the body of MET41 clinical study report Version 1.0 dated 11 September 2023 as outlined in this amendment as well as the CEO Version 1.0 dated 18 September 2023.** **In addition, a few transcriptional/typographic errors limited to the text in the CSR and CEO body (no**	Text added to provide rationale for programming discrepancy

Section Number / Heading	Summary of Changes	Rationale for Change
	changes in the data tables presented in the CSR Version 1.0) were also noted and were corrected. These are described in the Summary of Changes. **None of these corrections have an impact on the final conclusion of the study as provided in the CSR Version 1.0.**	

3.1.4.4	***Unsolicited AEs from D0 to D30- Overall SafAS*** There were ~~64.6~~ **65.0**% of subjects in Group 1 and ~~62.0~~ **62.7**% of subjects in Group 2 who reported at least 1 unsolicited AE within 30 days of vaccination. ***AESIs/MAAEs Within 30 Days- Overall SafAS*** Within 30 days of vaccination there were ~~1050~~ **1060** subjects (~~50.5~~ **51.0**%) in Group 1 and ~~334~~ **339** subjects (~~47.9~~ **48.6**%) in Group 2 who reported at least 1 MAAE. Corresponding table – Table 5 updated to reflect new results	Updated to reflect the outcome of the re-analysis
3.1.4.5	***Unsolicited AEs from D0 to D30 – SafAS1*** There were ~~28.0~~ **28.3**% of subjects in Group 1 and ~~26.4~~ **26.8**% of subjects in Group 2 who reported at least 1 unsolicited AE within 30 days of vaccination ***AESIs/MAAEs Within 30 Days – SafAS1*** Within 30 days of vaccination, there were ~~346~~ **351** subjects (~~16.6~~ **16.9**%) in Group 1 who reported 534 MAAEs and ~~115~~ **118** subjects (~~16.5~~ **16.9**%) in Group 2 who reported 167 MAAEs	Updated to reflect the outcome of the re-analysis

Section Number / Heading	Summary of Changes	Rationale for Change
	Corresponding table – Table 7 updated to reflect new results	

3.1.4.6	***Unsolicited AEs from D0 to D30 – SafAS2*** There were ~~32.0~~ **32.4**% of subjects in Group 1 and ~~28.8~~ **29.1**% of subjects in Group 2 who reported at least 1 unsolicited AE within 30 days of vaccination ***AESIs/MAAEs Within 30 Days – SafAS2*** Within 30 days of vaccination at 4 months of age, there were ~~438~~ **445** subjects (~~21.8~~ **22.2**%) in Group 1 and ~~128~~ **129** subjects (~~19.3~~ **19.5**%) in Group 2 who reported at least 1 MAAE Corresponding table – Table 9 updated to reflect new results	Updated to reflect the outcome of the re-analysis
3.1.4.7	***Unsolicited AEs from D0 to D30 – SafAS3*** There were ~~27.7~~ **28.0**% of subjects in Group 1 and ~~28.1~~ **28.7**% of subjects in Group 2 who reported at least 1 unsolicited AE within 30 days of vaccination ***AESIs/MAAEs Within 30 Days – SafAS3***	Updated to reflect the outcome of the re-analysis

Section Number / Heading	Summary of Changes	Rationale for Change
	Within 30 days of vaccination, there were ~~386~~ **392** subjects (~~19.8~~ **20.1**%) in Group 1 and ~~130~~ **134** subjects (~~20.1~~ **20.7**%) in Group 2 who reported at least 1 MAAE Corresponding table – Table 11 updated to reflect new results	

3.1.4.8	***Unsolicited AEs from D0 to D30 – SafAS4*** There were ~~38.5~~ **38.8**% of subjects in Group 1 and ~~33.9~~ **34.3**% of subjects in Group 2 who reported at least 1 unsolicited AE within 30 days of vaccination ***AESIs/MAAEs Within 30 Days – SafAS4*** Within 30 days of vaccination, there were ~~441~~ **447** subjects (~~24.0~~ **24.3**%) in Group 1 and ~~126~~ **129** subjects (~~20.2~~ **20.7**%) in Group 2 who reported at least 1 MAAE Corresponding table – Table 13 updated to reflect new results	Updated to reflect the outcome of the re-analysis
3.1.4.8	***Unsolicited ARs from D0 to D30 – SafAS4*** At least 1 unsolicited injection site AR rated as Grade 3 was reported in ~~3.9~~ **≤0.1**% of subjects in Group 1 and ~~3.7~~ **0.2**% of subjects in Group 2 within 30 days of vaccination	Transcription error, no changes to the data table
3.1.4.9	***Solicited reactions: injection site and systemic – SafAS5*** The proportion of subjects who reported at least 1 solicited injection site reaction for all 4-dose vaccination was ~~93.0~~ **87.1**% in Group 1 and ~~94.2~~ **86.2**% in Group 2	Transcription error, no changes to the data table

Section Number / Heading	Summary of Changes	Rationale for Change

3.1.4.9	***Unsolicited AEs from D0 to D30 – SafAS5*** There were ~~68.8~~ **69.2**% of subjects in Group 1 and ~~66.4~~ **67.2**% of subjects in Group 2 who reported at least 1 unsolicited AE within 30 days of vaccination ***AESIs/MAAEs Within 30 Days – SafAS5*** During the study, there were ~~993~~ **1002** subjects (~~54.1~~ **54.6**%) in Group 1 and ~~317~~ **322** subjects (~~51.0~~ **51.8**%) in Group 2 who reported at least 1 MAAE Corresponding table – Table 15 updated to reflect new results	Updated to reflect the outcome of the re-analysis
3.1.4.9	***Unsolicited ARs from D0 to D30 – SafAS5*** ~~The proportions of subjects who experienced at least 1 unsolicited injection site AR rated as Grade 3 within 30 days after the administration of a 4-dose vaccination of concomitant routine pediatric vaccines were as follows:~~ ~~For PENTACEL: 8.2% in Group 1 and 6.1% in Group 2.~~ ~~For PREVNAR 13: 9.4% in Group 1 and 8.8% in Group 2.~~	Data repeated in error

Section Number / Heading	Summary of Changes	Rationale for Change

	~~For ENGERIX B: 4.4% in Group 1 and 3.7% in Group 2.~~ ~~For M-M-R II: 2.9% in Group 1 and 1.9% in Group 2.~~ ~~For VARIVAX: 3.8% in Group 1 and 2.4% in Group 2.~~	

List of Changes from Clinical Study Report Version 1.0 Dated 11 September 2023 to Version 2.0 Dated 11 December 2023 (including the appendices)

Rational of the MET41 CSR Amendment 1:

Due to a programming discrepancy that had occurred during MET41 study statistical analysis, minor errors in the safety results were noted and have been corrected in the clinical study report (CSR).

- Unsolicited adverse events (AEs) with missing or partial missing dates that were previously not categorized as "occur within 30 days" are now considered as "occur within 30 days" and were added to the safety statistical analysis of "Unsolicited AE within 30 days after vaccination". This has increased the number of unsolicited non-serious AEs reported in the safety tables and presented the results in a more conservative way. All these AEs were non-serious and non- related to study products.
- The denominator (M) of the safety tables describing "All and related AEs leading to study discontinuation, by System Organ Class (SOC) and preferred terms (PT)" were wrongly computed and was updated using the definition "M: number of subjects in the safety analysis set". Numerators remained the same.

Those changes resulted in updates to relevant safety tables and the body of MET41 CSR Version 1.0 dated 11 September 2023 as outlined in the amendment. All changes are shown in the Redline of the CSR V1.0 to V2.0 included in the submission.

Minor typographical/transcriptional corrections unrelated to the amendment have been made in the CSR.

None of these corrections have an impact on the final conclusions of the study as provided in the CSR Version 1.0.

Document version	Date
Amended Final CSR version 2.0	**11 December 2023**
Final CSR version 1.0	11 September 2023

Section Number / Heading	Summary of Changes	Rationale for Change
Title Page	*Redline CSR: pages 1 and 2* **Report date:**	To reflect the CSR version number and date after the updates
Synopsis	*Redline CSR: pages 13, 14, 16, 17, 18, 19, 20, 21, 23, 25, and 26* The proportion of subjects who reported at least 1 unsolicited AEs has been updated for the SafAS, SafAS1, SafAS2, SafAS3, SafAS4 and SafAS5	To include the corrected information of the Amendment 1
	Redline CSR: pages 15, 17, 19, 21, 24, and 27 The numbers of subjects who reported at least 1 medically attended adverse event (MAAE) within 30 days of vaccination has been updated in the SafAS, SafAS1, SafAS2, SafAS3, SAfAS4 and SAfAS5	To include the corrected information of the Amendment 1
	Redline CSR: page 24 The proportions of subjects with at least 1 solicited injection site reactions in Groups 1 and 2 in the SafAS5 have been corrected	Transcriptional correction
	Redline CSR: page 27 The proportion of subjects impacted and not impacted by the COVID-19 pandemic situation has been corrected	To include the corrected information of the Amendment 1
	Redline CSR: page 28 The date and version of the report has been updated	To reflect the CSR version number and date after the updates

Section Number / Heading	Summary of Changes	Rationale for Change
	Date and Version of This Report: CSR version **2.0**~~1.0~~, dated **11 December 2023**~~11 September 2023~~	
	Redline CSR: page 29 The rational of the CSR amendment has been added	To include the corrected information of the Amendment 1
Section 4.1 Disposition of Subjects	*Redline CSR: page 56* The duration of the study has been corrected	Typographic correction
	Redline CSR: page 58 Figure 1 has been corrected (total number of planned subjects)	Typographic correction
Section 5.2.1 Safety Summary	*Redline CSR: pages 72 and 73* Table 6 (Section 8, Table 8.20) has been corrected	To include the corrected information of the Amendment 1
Section 5.2.1.1 Overall Population for any Vaccine Injections (SafAS)	*Redline CSR: pages 76 and 77* The proportions of subjects who reported at least 1 unsolicited (non-serious) AE and the number of subjects who reported at least 1 MAAE have been corrected (because of the Table 6 update)	To include the corrected information of the Amendment 1
Section 5.2.1.2 Subjects Aged 2 Months (SafAS1)	*Redline CSR: pages 79 and 80* The proportions of subjects who reported at least 1 unsolicited (non-serious) AE and the number of subjects who reported at least 1 MAAE have been corrected (because of the update of the Table 8.21 in Section 8)	To include the corrected information of the Amendment 1
Section 5.2.1.3 Subjects Aged 4 Months (SafAS2)	*Redline CSR: pages 81 and 82* The proportions of subjects who reported at least 1 unsolicited (non-serious) AE and the number of subjects who reported at least 1 MAAE have been corrected (because of the update of the Table 8.22 in Section 8)	To include the corrected information of the Amendment 1

Section Number / Heading	Summary of Changes	Rationale for Change

Section 5.2.1.4 Subjects Aged 6 Months (SafAS3)	*Redline CSR: pages 83 and 84* The proportions of subjects who reported at least 1 unsolicited (non-serious) AE and the number of subjects who reported at least 1 MAAE have been corrected (because of the update of the Table 8.23 in Section 8)	To include the corrected information of the Amendment 1
Section 5.2.1.5 Subjects Aged 12 Months (SafAS4)	*Redline CSR: pages 86 and 87* The proportions of subjects who reported at least 1 unsolicited (non-serious) AE and the number of subjects who reported at least 1 MAAE have been corrected (because of the update of the Table 8.24 in Section 8)	To include the corrected information of the Amendment 1
Section 5.2.1.6 Subjects who Received all 4-dose Vaccination (SafAS5)	*Redline CSR: page 87* The proportions of subjects with at least 1 solicited injection site reactions in Groups 1 and 2 in the SafAS5 have been corrected	Transcriptional correction
	Redline CSR: pages 88, 89 and 90 The proportions of subjects who reported at least 1 unsolicited (non-serious) AE and the number of subjects who reported at least 1 MAAE have been corrected (because of the update of the Table 8.25 in Section 8)	To include the corrected information of the Amendment 1
Section 5.2.2.1.1.1 Solicited Injection Site Reactions	*Redline CSR: page 95* Grammatical/typographical corrections have been made to the description of the Grade 3 solicited injection site reactions	Typographic correction
Section 5.2.2.1.1.2 Solicited Systemic Reactions	*Redline CSR: page 104* Grammatical/typographical corrections have been made to the description of the Grade 3 solicited injection site reactions	Typographic correction
Section 5.2.2.1.2.1 Unsolicited AEs	*Redline CSR: pages 109, 110 and 111*	To include the corrected information of the Amendment 1

Section Number / Heading	Summary of Changes	Rationale for Change
	Data relative to unsolicited AEs in the SafAS have been corrected (because of the update of the Table 13 [Section 8, Table 8.100], and Table 8.88 and Table 8.92 in Section 8)	

	Redline CSR: pages 112 to 129 Table 13 (Section 8, Table 8.100) has been corrected	To include the corrected information of the Amendment 1
Section 5.2.2.1.2.2 Unsolicited ARs	*Redline CSR: page 130* The sentences presenting tables in Section 8 have been reworded	To improve the clarity of the text
	Redline CSR: page 130 Grammatical/typographical corrections have been made to the description of the unsolicited ARs	Typographic correction
	Redline CSR: page 130 The sentence describing the absence of ARs for Rotateq has been deleted	ARs were not collected for Rotateq (oral vaccine)
Section 5.2.2.2.1.1 Solicited Injection Site Reactions in Subjects Aged 2 Months	*Redline CSR: pages 136 and 137* Grammatical/typographical corrections have been made to the description of the Grade 3 solicited injection site reactions	Typographic correction
Section 5.2.2.2.1.2 Solicited Systemic Reactions in Subjects Aged 2 Months	*Redline CSR: page 144* The incidence of appetite lost has been corrected for Group 1 and Group 2	Transcriptional correction
	Redline CSR: page 144 Grammatical/typographical corrections have been made to the description of the Grade 3 systemic reactions	Typographic correction
Section 5.2.2.2.2.1 Unsolicited AEs in Subjects Aged 2 Months	*Redline CSR: page 149* Data relative to unsolicited AEs in the SafAS1 have been corrected (because of the update of the Table 19 [Section 8, Table 8.180] and Table 8.74 and Table 8.176 in Section 8)	To include the corrected information of the Amendment 1

Section Number / Heading	Summary of Changes	Rationale for Change
	Redline CSR: pages 150 to 158 Table 19 (Section 8, Table 8.180) has been corrected	To include the corrected information of the Amendment 1

Section 5.2.2.2.2.2 Unsolicited ARs in Subjects Aged 2 Months	*Redline CSR: page 159* The sentences presenting tables in Section 8 have been reworded	To improve the clarity of the text
	Redline CSR: page 159 Grammatical/typographical corrections have been made to the description of unsolicited adverse reactions (ARs)	Typographic correction
	Redline CSR: page 160 The incidence of gastrointestinal disorders has been corrected	Transcriptional correction
Section 5.2.2.3.1.1 Solicited Injection Site Reactions in Subjects Aged 4 Months	*Redline CSR: pages 164* Incidences of Grade 3 solicited injection site reactions have been corrected	Transcriptional correction
	Redline CSR: pages 164 Grammatical/typographical corrections have been made to the description of the Grade 3 solicited injection site reactions	Typographic correction
Section 5.2.2.3.1.2 Solicited Systemic Reactions in Subjects Aged 4 Months	*Redline CSR: page 169* Incidences of irritability in Group 1 and of Grade 3 solicited injection site reactions have been corrected	Transcriptional correction
Section 5.2.2.3.2.1 Unsolicited AEs in Subjects Aged 4 Months	*Redline CSR: pages 174 and 175* Data relative to unsolicited AEs in the SafAS2 have been corrected (because of the update of the Table 25 [Section 8, Table 8.181], and Table 8.175 and Table 8.177 in Section 8)	To include the corrected information of the Amendment 1

Section Number / Heading	Summary of Changes	Rationale for Change
	Redline CSR: pages 176 to 184 Table 25 (Section 8, Table 8.181) has been corrected	To include the corrected information of the Amendment 1
Section 5.2.2.3.2.2 Unsolicited ARs in Subjects Aged 4 Months	*Redline CSR: page 185* The sentences presenting tables in Section 8 have been reworded	To improve the clarity of the text

	Redline CSR: page 185 Grammatical/typographical corrections have been made to the description of the unsolicited ARs	Typographic correction
	Redline CSR: page 185 Incidence of unsolicited ARs and Grade 3 unsolicited ARs for Menveo (Group 2) has been corrected	Transcriptional correction
Section 5.2.2.4.1.1 Solicited Injection Site Reactions in Subjects Aged 6 Months	*Redline CSR: pages 190 and 191* Grammatical/typographical corrections have been made to the description of the Grade 3 solicited injection site reactions	Typographic correction
Section 5.2.2.4.1.2 Solicited Systemic Reactions in Subjects Aged 6 Months	*Redline CSR: page 198* Grammatical/typographical corrections have been made to the description of the Grade 3 systemic reactions	Typographic correction
Section 5.2.2.4.2.1 Unsolicited AEs in Subjects Aged 6 Months	*Redline CSR: pages 203 and 204* Data relative to unsolicited AEs in the SafAS3 have been corrected (because of the update of the Table 31 [Section 8, Table 8.101], and Table 8.89 and Table 8.93 in Section 8)	To include the corrected information of the Amendment 1
	Redline CSR: pages 205 to 212 Table 31 (Section 8, Table 8.101) has been corrected	To include the corrected information of the Amendment 1

Section Number / Heading	Summary of Changes	Rationale for Change
Section 5.2.2.4.2.2 Unsolicited ARs in Subjects Aged 6 Months	*Redline CSR: page 203* The sentences presenting tables in Section 8 have been reworded	To improve the clarity of the text
	Redline CSR: page 203 Grammatical/typographical corrections have been made to the description of unsolicited ARs	Typographic correction
	Redline CSR: page 213 The sentence describing the absence of ARs for Rotateq has been deleted	ARs were not collected for Rotateq (oral vaccine)

	Redline CSR: page 214 The sentences describing the absence of ARs for M-M-M II and VARIVAX vaccines have been deleted	Those vaccines were not administered at this visit
Section 5.2.2.5.1.1 Solicited Injection Site Reactions in Subjects Aged 12 Months	*Redline CSR: pages 219 and 220* Grammatical/typographical corrections have been made to the description of the Grade 3 solicited injection site reactions	Typographic correction
Section 5.2.2.5.1.2 Solicited Systemic Reactions in Subjects Aged 12 Months	*Redline CSR: page 227* Grammatical/typographical corrections have been made to the description of the Grade 3 systemic reactions	Typographic correction
Section 5.2.2.5.2.1 Unsolicited AEs in Subjects Aged 12 Months	*Redline CSR: pages 232 and 233* Data relative to unsolicited AEs in the SafAS4 have been corrected (because of the update of the Table 37 [Section 8, Table 8.102], and Table 8.90 and Table 8.94 in Section 8)	To include the corrected information of the Amendment 1
	Redline CSR: pages 234 to 242 Table 37 (Section 8, Table 8.102) has been corrected	To include the corrected information of the Amendment 1

Section 5.2.2.5.2.2 Unsolicited ARs in Subjects Aged 12 Months	*Redline CSR: page 243* The sentences presenting tables in Section 8 have been reworded	To improve the clarity of the text
	Redline CSR: page 243 Grammatical/typographical corrections have been made to the description of the unsolicited ARs	Typographic correction
	Redline CSR: page 243 The sentence describing the absence of ARs for Rotateq has been deleted	ARs were not collected for Rotateq (oral vaccine)
	Redline CSR: pages 243 and 244 The sentences describing the absence of ARs for PENTACEL and ENGERIX vaccines have been deleted	Those vaccines were not administered at this visit

Section 5.2.2.6.1.1 Solicited Injection Site Reactions in Subjects who Received All 4-dose Vaccinations	*Redline CSR: pages 245 to 247* The sentence for the ongoing solicited injection site reactions has been corrected	Typographic correction
	Redline CSR: pages 247 and 248 Grammatical/typographical corrections have been made to the description of the Grade 3 solicited injection site reactions	Typographic correction
Section 5.2.2.6.1.2 Solicited Systemic Reactions in Subjects who Received All 4-dose Vaccinations	*Redline CSR: page 248* The incidence of crying abnormal has been corrected	Transcriptional correction
	Redline CSR: page 249 The incidence of Grade 3 solicited systemic reactions has been corrected	Transcriptional correction
Section 5.2.2.6.2.1 Unsolicited AEs in Subjects who Received All 4-dose Vaccinations	*Redline CSR: pages 250 and 251* Data relative to unsolicited AEs in the SafAS5 have been corrected (because of the update of the Table 8.91, Table 8.95, Table 8.103 in Section 8)	To include the corrected information of the Amendment 1

Section 5.2.2.6.2.2 Unsolicited ARs in Subjects who Received All 4-dose Vaccinations	*Redline CSR: page 251* The sentences presenting tables in Section 8 have been reworded	Typographic correction
	Redline CSR: pages 251 to 253 Grammatical/typographical corrections have been made to the description of unsolicited ARs	Typographic correction
Section 5.2.2.9 Discontinuation due to Adverse Events	*Redline CSR: pages 256 and 257* Data relative to discontinuations due to AEs have been corrected (because of the update of the Table 8.116, Table 8.117, and Table 8.119 in Section 8)	To include the corrected information of the Amendment 1
Section 5.2.2.11 Other Significant Adverse Events	*Redline CSR: pages 258 to 263* Data relative to other significant AEs have been corrected (because of the update of the Table 8.139, Table 8.140, and Table 8.143 in Section 8)	To include the corrected information of the Amendment 1
Section 5.3.1.2 Impact of COVID-19 Pandemic on Safety Overview After any Vaccine Injections	*Redline CSR: page 267* Data relative to other significant AEs have been corrected (because of the update of the Table 3 and Table 4 in Appendix 15)	To include the corrected information of the Amendment 1

Section 5.3.3 Safety Analyses by Race	*Redline CSR: pages 267 and 268* Data relative to other significant AEs have been corrected (because of the update of the Table 7 and Table 9 in Appendix 15)	To include the corrected information of the Amendment 1
Synopsis and body	Minor typographic errors have been corrected	Typographic correction
	Redline CSR: pages 14, 16, 18, 20, 21, 23, 25, 76, 79, 81, 83, 84, 86, 88 Redundant data (presented twice) have been removed (unsolicited AEs and ARs)	Typographic correction
Section 8	The following tables have been updated: - **Table 8.20**: Safety overview after vaccine injection - Overall Safety Analysis Set for Any Dose • **Table 8.21**: Safety overview after vaccine injection at 2 Months of Age - Safety Analysis Set 1 • **Table 8.22**: Safety overview after vaccine injection at 4 Months of Age - Safety Analysis Set 2 • **Table 8.23**: Safety overview after vaccine injection at 6 Months of Age - Safety Analysis Set 3 • **Table 8.24**: Safety overview after vaccine injection at 12 Months of Age - Safety Analysis Set 4 • **Table 8.25**: Safety overview after vaccine injection - Safety Analysis Set for all 4-Dose Vaccination • **Table 8.88**: Summary of unsolicited AEs within 30 days after vaccine injections - Overall Safety Analysis Set for Any Dose • **Table 8.89**: Summary of unsolicited AEs within 30 days after vaccine injections at 6 Months of Age - Safety Analysis Set 3 • **Table 8.90**: Summary of unsolicited AEs within 30 days after vaccine injections at 12 Months of Age - Safety Analysis Set 4 • **Table 8.91**: Summary of unsolicited AEs within 30 days after vaccine injections - Safety Analysis Set for all 4-Dose Vaccination	To include the corrected information of the Amendment 1

	• **Table 8.92**: Unsolicited AEs within 30 days after vaccine injections, by maximum intensity, time of onset, and duration - Overall Safety Analysis Set for Any Dose • **Table 8.93**: Unsolicited AEs within 30 days after vaccine injections at 6 Months of Age, by maximum intensity, time of onset, and duration - Safety Analysis Set 3 • **Table 8.94**: Unsolicited AEs within 30 days after vaccine injections at 12 Months of Age, by maximum intensity, time of onset, and duration - Safety Analysis Set 4 • **Table 8.95**: Unsolicited AEs within 30 days after vaccine injections, by maximum intensity, time of onset, and duration - Safety Analysis Set for all 4-Dose Vaccination • **Table 8.100**: Unsolicited AEs within 30 days after vaccine injections, by system organ class and preferred term - Overall Safety Analysis Set for Any Dose • **Table 8.101**: Unsolicited AEs within 30 days after vaccine injections at 6 Months of Age, by system organ class and preferred term - Safety Analysis Set 3 • **Table 8.102**: Unsolicited AEs within 30 days after vaccine injections at 12 Months of Age, by system organ class and preferred term - Safety Analysis Set 4 • **Table 8.103**: Unsolicited AEs within 30 days after vaccine injections, by system organ class and preferred term - Safety Analysis Set for all 4-dose vaccination • **Table 8.116**: All and related AEs leading to study discontinuation, by system organ class and preferred term - Overall Safety Analysis Set for Any Dose • **Table 8.117**: All and related AEs leading to study discontinuation after vaccine injections at 6 Months of Age, by system organ class and preferred term - Safety Analysis Set 3	

	• **Table 8.118**: All and related AEs leading to study discontinuation after vaccine injections at 12 Months of Age, by system organ class and preferred term - Safety Analysis Set 4 • **Table 8.119**: All and related AEs leading to study discontinuation after vaccine injections, by system organ class and preferred term - Safety Analysis Set for all 4-Dose Vaccination • **Table 8.139**: MAAEs within 7 days after vaccine injection, by maximum intensity, time of onset, and duration - Overall Safety Analysis Set for Any Dose • **Table 8.140**: MAAEs within 30 days after vaccine injection, by maximum intensity, time of onset, and duration - Overall Safety Analysis Set for Any Dose • **Table 8.142**: All and related MAAEs within 7 days after vaccine injections, by system organ class and preferred term - Overall Safety Analysis Set for Any Dose	

	• **Table 8.143**: All and related MAAEs within 30 days after vaccine injections, by system organ class and preferred term - Overall Safety Analysis Set for Any Dose • **Table 8.174**: Summary of unsolicited AEs within 30 days after vaccine injections at 2 Months of Age - Safety Analysis Set 1 • **Table 8.175**: Summary of unsolicited AEs within 30 days after vaccine injections at 4 Months of Age - Safety Analysis Set 2 • **Table 8.176**: Unsolicited AEs within 30 days after vaccine injections at 2 Months of Age, by maximum intensity, time of onset, and duration - Safety Analysis Set 1 • **Table 8.177**: Unsolicited AEs within 30 days after vaccine injections at 4 Months of Age, by maximum intensity, time of onset, and duration - Safety Analysis Set 2 • **Table 8.180**: Unsolicited AEs within 30 days after vaccine injections at 2 Months of Age, by system organ class and preferred term - Safety Analysis Set 1 • **Table 8.181**: Unsolicited AEs within 30 days after vaccine injections at 4 Months of Age, by system organ class and preferred term - Safety Analysis Set 2 • **Table 8.188**: All and related AEs leading to study discontinuation after vaccine injections at 2 Months of Age, by system organ class and preferred term - Safety Analysis Set 1 • **Table 8.189**: All and related AEs leading to study discontinuation after vaccine injections at 4 Months of Age, by system organ class and preferred term - Safety Analysis Set 2	
Appendix 5	Update of information on service provider	Administrative change, no data changes
Appendix 6	The signatures of the Principal Investigator and Sponsor's Responsible Medical Officer were collected for the Version 2.0 of the CSR	To include the corrected information to Amendment 1
Appendix 15	The following tables have been updated:	To include the corrected information to Amendment 1

	• **Table 3**: Impact of COVID-19 pandemic on safety overview after vaccine injection - Subjects from Overall Safety Analysis Set for Any Dose impacted by COVID-19 pandemic situation • **Table 4**: Impact of COVID-19 pandemic on safety overview after vaccine injection - Subjects from Overall Safety Analysis Set for Any Dose not impacted by COVID-19 pandemic situation • **Table 5**: Safety overview after any vaccine injections by gender - female subjects - Overall Safety Analysis Set for Any Dose • **Table 6**: Safety overview after any vaccine injections by gender - male subjects - Overall Safety Set for Any Dose • **Table 7**: Safety overview after any vaccine injections by race - White subjects - Overall Safety Analysis for Any Dose • **Table 8**: Safety overview after any vaccine injections by race - Asian subjects - Overall Safety Analysis Set for Any Dose • **Table 9**: Safety overview after any vaccine injections by race - Black or African American subjects - Overall Safety Analysis Set for Any Dose • **Table 11**: Safety overview after vaccine injections by preterm and full-term birth within Group 1 - Overall Safety Analysis for Any Dose • **Table 13**: Summary of unsolicited AEs within 30 days after vaccine injections by preterm and full-term birth within Group 1 - Overall Safety Analysis Set for Any Dose	
Appendix 16	The **Listing 5.4** Unsolicited adverse events not included in the Safety Analysis has been updated	To include the corrected information to Amendment 1

Rapporteur's assessment and conclusion:

The rational for the MET41 CSR Amendment is acknowledged. Unsolicited AEs within 30 days are now also included when missing or partial missing dates were recorded and the denominator (M) of the safety tables describing "All and related AEs leading to study discontinuation, by System Organ Class (SOC) and preferred terms (PT)" was implemented in its correct definition (i.e. M: number of subjects in the safety analysis set). The provided corrected data were included in this updated assessment report and do not alter the original conclusion.

The fact that AEs were erroneously reported raises concerns on the integrity of study MET41 and raises the question about the correct reporting of AEs for other studies included in the planned variation. The Applicant is asked to perform a root-cause analysis and to outline measures to identify such issues in submitted and ongoing MenQuadfi studies as well as to prevent such errors in future submissions (OC).

2nd MAH responses to Request for supplementary information

Question:

The fact that AEs were erroneously reported raises concerns on the integrity of study MET41 and raises the question about the correct reporting of AEs for other studies included in the planned variation. The Applicant is asked to perform a root-cause analysis and to outline measures to identify such issues in submitted and ongoing MenQuadfi studies as well as to prevent such errors in future submissions (OC).

MAH response:

As communicated in the answer to Request for Supplementary Information received on 14 December 2023, the discrepancy in the analyses of unsolicited AEs were due to the following two reasons:

1. Unsolicited AEs with missing or partially missing dates, preventing proper classification, were previously not categorized as "occur within 30 days" but were listed and described in Appendix 16.5, listing 5.1. These unsolicited AEs with missing or partially missing dates are now considered as "occur within 30 days" and are included in the safety statistical analysis of "Unsolicited AE within 30 days after vaccination". This increases the number of unsolicited non-serious AEs reported in the safety tables by a total of 59 cases, presenting the results in a more conservative way. All these AEs were non-serious and non-related to study products.

2. The denominator (M) of the safety tables describing "All and related AEs leading to study discontinuation, by System Organ Class (SOC) and Preferred Term (PT)" are updated using the definition "M: number of subjects in the safety analysis set". All numerators remain the same. This update ensures the denominators of corresponding tables are consistent with the denominators used in other safety analysis tables.

Other previously submitted clinical studies in the frame of a variation or Article 46 (MET62, MEQ00065, MET59, MEQ00066 stage I, MET52, MEQ00071, MET33) were not impacted by the above issues. For statistical analyses of other studies to be submitted later, preventive measures have been implemented and will prevent such errors in future submissions.

Applicant would like to confirm that despite the discrepancy in the analyses, AE reporting of MET41 study was not impacted. AEs were reported correctly according to MET41 study protocol and Sanofi safety guidelines for clinical trials.

A complementary answer on root-cause analysis and preventive measures is provided hereafter.

Root cause analysis

The root cause of the two observations above leading to the update in the MET41 Clinical Study Report (CSR) were due to programming's different understanding of the derivation rules used in those AE analyses and the specific context of the study.

In the general statistical analysis plan template, in order to cover all study types and situations, there are several options available for analyzing a particular endpoint. In MET41, the original statistical analysis plan for Tables, Listings and Figures (TLF) of Statistical Analysis Plan (SAP) didn't specify the correct denominator, which caused the programmers to use a different derivation rule from what was intended by the study statistician and generally used in other studies.

Preventive measures

1) Internal statistical analysis plan template is now updated with more detailed instructions and examples, on how to deal with missing/partially missing dates. Please see the appendix below for more details.

2) Related trainings for these standard derivation rules will be conducted and will be reinforced in the onboarding program for new programmers and statisticians.

3) Statisticians are instructed to put more detailed instructional specifications in the statistical analysis plan or related document for programming team, to avoid any possible misunderstanding.

Appendix: Instruction wording recently added in Sanofi's internal standard safety analysis template (January 2024) to prevent future issue of similar kind

- For unsolicited AE with missing day, month and year, the unsolicited AE will be classified as "Within 30 days"
- For unsolicited AE with partially missing start date, the partial available information will be used to determine if this AE is classified "Within 30 days" or "Not within 30 days". An AE will be categorized as "Not within 30 days" only if there is clear evidence from the partially missing start date that this AE happens before the first vaccination or after the last vaccination + 30 days. In all other situations, this AE is considered as "Within 30 days". Situations may happen as:
    - If the start date of AE has missing Day and non-missing Month and Year
        - If the "Month/Year of AE start date" < "Month/Year of first vaccination date", then it is clear that this unsolicited AE happened before the first vaccination and this unsolicited AE will not be included in the analysis but will be listed separately.
        - Else if the "Month/Year of last vaccination date" <= "Month/Year of AE start date" <= "Month/Year of (last vaccination date + 30 days)", then this unsolicited AE will be categorized as "Within 30 days".
        - Else if the "Month/Year of AE start date" > "Month/Year of (last vaccination date + 30 days)", then this unsolicited AE will be categorized as "not within 30 days". If the AE is non-serious, non-AESI and non-MAAE, then it will not be included in the analysis but will be listed separately.
    - If the start date of AE has missing Day and Month and non-missing Year:
        - If the "Year of AE start date" < "Year of first vaccination date", then it is clear that this unsolicited AE happens before the first vaccination and this unsolicited AE will not be included in the analysis but will be listed separately.
        - Else if the "Year of last vaccination date" <= "Year of AE start date" <= "Year of (last vaccination date + 30 days)", then this unsolicited AE will be categorized as "Within 30 days".
        - Else if the "Year of AE start date" > "Year of (last vaccination date + 30 days)", then this unsolicited AE will be categorized as "not within 30 days". If the AE is non-serious, non-AESI and non-MAAE, then it will not be included in the analysis but will be listed separately.

A few examples of missing time of onset with start date of AE partially missing:

First injection date	Last injection date	Start date of the AE	Injection date + 30	Will be analyzed "Within 30 days"?
16Oct2023	16Oct2023	Missing	N/A	Y
16Oct2023	16Oct2023	Sep2023	N/A	N
16Oct2023	16Oct2023	Oct2023	15Nov2023	Y
16Oct2023	16Oct2023	Nov2023	15Nov2023	Y
16Oct2023	16Oct2023	Dec2023	15Nov2023	N
05Jan2023	05Jan2023	2022	N/A	N
16Oct2023	16Oct2023	2023	15Nov2023	Y
08Dec2023	08Dec2023	2024	07Jan2024	Y
16Oct2023	16Oct2023	2024	15Nov2023	N

Rapporteur's assessment and conclusion:

The MAH clarified that other previously submitted clinical studies in the frame of a variation or Article 46 (MET62, MEQ00065, MET59, MEQ00066 stage I, MET52, MEQ00071, MET33) were not impacted by the statistical issues of study MET41.

The provided root cause analysis explained why erroneous data was submitted initially for study MET41.

For the statistical analyses of future studies, preventive measures such as the update of the MAH´s internal statistical analysis plan template and specific internal trainings have been implemented. These measures are considered adequate to avoid the methodological issues of MET41 in future submissions.

Issue resolved. No further actions required.

4. Rapporteur's overall conclusion and recommendation

At present, the study population of MET41 is not covered by the EU Marketing Authorisation of MenQuadfi, which is currently indicated in the EU from the age of 12 months and older. The purpose of MET41 was to describe the safety profile of the MenACYW conjugate vaccine and the comparator MENVEO when administered in 4 doses concomitantly with routine paediatric vaccines given to healthy infants and toddlers between 6 weeks of age and 12 months of age.

The submitted results of study MET41 comprised descriptive safety data sets summarizing AEs that occurred during the study at different age (dose 1-4). Overall, the data indicate a safety profile of MenQuadfi that is roughly comparable to the comparator vaccine MENVEO, when administered concomitantly with routine paediatric vaccines in healthy infants and toddlers 2 to 12 months of age. However, the adequacy of Menveo as comparator vaccine is questionable as Menveo is not licensed for the respective age group in the EU. This aspect requires further elaboration for any future variation application. Similarly, the use of administered concomitant vaccines should be justified based on EU standards (i.e. licensure of vaccines used and vaccine schedule). Furthermore, serious adverse events (especially those related to lower respiratory tract infections as well as seizures/convulsions) should be assessed in detail once all data of the clinical program in subjects <12 years become available.

Study MET41 is part of the MenQuadfi Paediatric Investigational Plan, EMA procedure number: EMEA-001930-PIP01-16-M04). The MAH´s plan is to complete all the ongoing paediatric clinical studies MET33, MET41, MET42, MET52, MET58, MET61 covering 6 weeks to 12 months population prior to submit all the data together under a type II variation with product information update all the data together to support the extension of indication for use of MenQuadfi in individuals from the age of 6

weeks and older (planned submission Q1 2025 in the EU). As discussed above, data from the complete developmental program are considered of high relevance for the risk assessment in toddlers, especially with respect to observed deaths and serious adverse events.

After finalisation of this report, the MAH communicated errors in the currently provided documentation of this article 46 standalone procedure for MET41. The respective information was updated after request of the corrected information.

Furthermore, the MAH clarified that other previously submitted clinical studies in the frame of a variation or Article 46 (MET62, MEQ00065, MET59, MEQ00066 stage I, MET52, MEQ00071, MET33) were not impacted by the statistical issues of study MET41.

For the statistical analyses of future studies, preventive measures such as the update of the MAH´s internal statistical analysis plan template and specific internal trainings have been implemented. These measures are considered adequate to avoid the methodological issues of MET41 in future submissions.

☒ Fulfilled:

No regulatory 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	Q4 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	Expected in October 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	Expected in October 2023	Q2 2024