25 July 2024
EMA/308452/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006

MenQuadfi

Meningococcal Group A, C, W and Y conjugate vaccine

Procedure no: EMEA/H/C/005084/P46/012

Note

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

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	27/05/2024	27/05/2024
☐	CHMP Rapporteur Assessment Report	01/07/2024	01/07/2024
☐	CHMP members comments	15/07/2024	15/07/2024
☐	Updated CHMP Rapporteur Assessment Report	18/07/2024	N/A
☒	CHMP adoption of conclusions:	25/07/2024	25/07/2024

Table of contents

1. Introduction

On 6 May 2024, 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 MET61 "An immunogenicity and safety study of a quadrivalent meningococcal conjugate vaccine administered concomitantly with routine paediatric 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 to 12 months population: MET33, MET41, MET42, MET52, MET58, MET61) is expected to be submitted in Q1 2025. A line listing of all the concerned studies is annexed.

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 MET61**: An immunogenicity and safety study of a quadrivalent meningococcal conjugate vaccine administered concomitantly with routine paediatric vaccines in healthy infants and toddlers.

2.3.2. Clinical study MET61

Description

Study MET61 is a Phase III, randomised, parallel group, active-controlled, multi-centre study to compare the immunogenicity and describe the safety of MenACYW conjugate vaccine and Menveo when administered in a 1 + 1 schedule and concomitantly with routine paediatric vaccines in healthy infants and toddlers in the US. This study also describes the safety and immunogenicity of MenACYW conjugate vaccine and Menactra when administered in a 1 +1 schedule to healthy toddlers in the US. For each age group at enrolment, the study had a modified double-blind design, i.e., modified double-blind between Group 1 and Group 2, and between Group 3 and Group 4.

This study was conducted at 47 centres that enrolled and randomised subjects in the US and Puerto Rico.

The study was conducted between 04 October 2018 (first subject first visit) and 23 October 2023 (last subject last contact).

Methods

Study participants

Approximately 1070 healthy infants were planned to be randomised. The study population was planned to include 870 healthy infants 6 to 7 months of age, and 200 healthy toddlers 17 to 19 months of age.

Inclusion Criteria

An individual must fulfil all of the following criteria to be eligible for study enrolment:

1) Aged 6 to 7 months (168 to 224 days) or 17 to 19 months on the day of the first visit;
2) Informed consent form has been signed and dated by the parent(s) or other guardian and by an independent witness if required by local regulations;
3) Subject and parent/guardian are able to attend all scheduled visits and to comply with all trial procedures;
4) For subjects 6 to 7 months of age at enrolment (Group 1 and Group 2), documented history of having received 2 doses of DTaP, Hib, IPV, pneumococcal, hepatitis B (for children who received Pediarix at 2 and 4 months of age, prior receipt of 3 doses of hepatitis B), and rotavirus (Rotateq) vaccines;
5) For subjects to be enrolled at 17 to 19 months of age (Group 3 and Group 4), documented history of having received all routine paediatric vaccines recommended by ACIP up to the age.

Exclusion Criteria

An individual fulfilling any of the following criteria is to be excluded from study enrolment:

1) Participation at the time of study enrolment 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) Receipt of any vaccine in the 4 weeks preceding the first trial vaccination or planned receipt of any vaccine in the 4 weeks before and / or following any trial vaccination except for influenza vaccination, which may be received at least 2 weeks before or 2 weeks after any study vaccination. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines;
3) Previous vaccination against meningococcal disease with either the trial vaccine or another vaccine (i.e., mono- or polyvalent, PS, or conjugate meningococcal vaccine containing serogroups A, C, Y, or W; or meningococcal B serogroup-containing vaccine);
4) For subjects to be enrolled at 6 to 7 months of age (Group 1 and Group 2), prior receipt of more than 2 doses of rotavirus vaccine (Rotateq), DTaP, Hib, IPV, pneumococcal, hepatitis B; for children who received Pediarix at 2 and 4 months of age, prior receipt of more than 3 doses of hepatitis B vaccine;
5) For subjects to be enrolled at 6 to 7 months of age (Group 1 and Group 2), receipt of 2 doses of rotavirus vaccine, Rotarix at 2 and 4 months of age;
6) Receipt of immune globulins, blood, or blood-derived products in the past 3 months;
7) Known or suspected congenital or acquired immunodeficiency or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy within the preceding 6

months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks) within the past 3 months;

8) Family history of congenital or hereditary immunodeficiency, until the immune competence of the potential vaccine recipient is demonstrated;

9) Individuals with blood dyscrasias, leukaemia, lymphoma of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems;

10) Individuals with active tuberculosis;

11) History of any Neisseria meningitidis infection, confirmed either clinically, serologically, or microbiologically;

12) 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;

13) At high risk for meningococcal infection during the trial (specifically, but not limited to, subjects with persistent complement deficiency, with anatomic or functional asplenia, or subjects travelling to countries with high endemic or epidemic disease);

14) History of intussusception;

15) History of any neurologic disorders, including any seizures and progressive neurologic disorders;

16) History of Arthus-type hypersensitivity reaction after a previous dose of tetanus toxoid containing vaccine;

17) History of Guillain-Barré syndrome;

18) Known systemic hypersensitivity to any of the vaccine components or to latex, or history of a life-threatening reaction to the vaccine(s) used in the trial or to a vaccine containing any of the same substances, including neomycin, gelatine, and yeast;

19) Verbal report of thrombocytopenia contraindicating intramuscular vaccination in the investigator's opinion;

20) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination in the investigator's opinion;

21) Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw;

22) Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with trial conduct or completion;

23) Any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives;

24) Moderate or severe acute illness/infection (according to investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided;

25) Identified as a natural or adopted child of the investigator or employee with direct involvement in the proposed study.

If the subject has a primary physician who is not the Investigator, the site must contact the physician with the parent's / guardian's consent to inform him / her of the subject's participation in the study. In addition, the site should ask this primary physician to verify exclusion criteria relating to previous therapies, such as receipt of blood products or previous vaccines.

Treatments

Group 1: MenACYW conjugate vaccine + routine paediatric vaccines at 6 to 7 months of age and 12 to 13 months of age.

Group 2: MENVEO + routine paediatric vaccines at 6 to 7 months of age and 12 to 13 months of age.

Group 3: MenACYW conjugate vaccine at 17 to 19 months of age and 20 to 23 months of age.

Group 4: Menactra at 17 to 19 months of age and 20 to 23 months of age.

All subjects in Group 1 and Group 2 were to receive a dose of either MenACYW conjugate vaccine or MENVEO with the following routine paediatric vaccines to ensure compliance with the Advisory Committee on Immunization Practices (ACIP) recommendations:

- Diphtheria, tetanus and acellular pertussis (DTaP) at 6 months of age;
- Inactivated poliovirus (IPV) at 6 months of age;
- *Haemophilus influenzae* type b (Hib) at 6 months of age (In children immunized with PedvaxHIB at 2 and 4 months of age, a third dose of Hib vaccine at 6 months of age was not required);
- Pneumococcal 13-valent conjugate vaccine (Prevnar 13, PCV13) at 6 and 13 months of age;
- Rotavirus (RotaTeq) at 6 months of age;
- Hepatitis B at 6 months of age;
- Measles, mumps, and rubella (M-M-RII) at 12 months of age;
- Varicella (Varivax) at 12 months of age.

The routine paediatric vaccines recommended at 6 months of age were to be given as per standard of care during the first study visit (Visit 1) along with the corresponding study vaccine. The dose of Prevnar 13 and Hib (for children vaccinated with monovalent Hib vaccine at 2, 4, and 6 months of age) recommended in the second year of life should be given as per standard of care at the last study visit after completing all the study procedures (Visit 4). Routine paediatric vaccines recommended at 6 months of age and the dose of Prevnar 13 and Hib (for children vaccinated with monovalent Hib vaccine at 2, 4, and 6 months of age) recommended in the second year of life were not provided by the Sponsor but procured by the sites as per their standard practices.

Blood Sampling

All participants in Group 1 and Group 2 were to provide 3 blood samples for immunogenicity assessment:

- A blood sample before the first study vaccination at Visit 1 (all participants);
- A blood sample 30 days after administration of the first dose of MenACYW conjugate vaccine or MENVEO at Visit 2 (the first 50% of the participants in Group 1 and Group 2);
- A blood sample before the 12-month vaccination at Visit 3 (the remaining 50% of participants in Group 1 and Group 2, who did not have a blood draw at Visit 2);

- A blood sample 30 days after administration of the second dose of MenACYW conjugate vaccine or MENVEO at Visit 4 (all participants in Group 1 and Group 2).

All participants in Group 3 and Group 4 were to provide 2 blood samples for immunogenicity assessment:

- A blood sample before the first study vaccination at Visit 1;
- A blood sample 30 days after administration of the second dose of MenACYW conjugate vaccine or Menactra at Visit 3.

Table 1: Vaccination and blood sampling schedule - Group 1 and Group 2

Age in months	**6 to 7 months**		**7 to 8 months**	**12 months**		**13 months**	
Visit #	Visit 1		Visit 2	Visit 3		Visit 4	
Procedure	**Blood Draw***	**Vaccines†**	**Blood Draw‡**	**Blood Draw§**	**Vaccines**	**Blood Draw**	**Vaccines****
Group 1	X	**MenACYW** DTaP IPV Hib PCV13 Rotavirus HB	X	X	**MenACYW** MMR Varicella	X	PCV13 Hib
Group 2	X	**MENVEO** DTaP IPV Hib PCV13 Rotavirus HB	X	X	**MENVEO** MMR Varicella	X	PCV13 Hib

* Blood will be drawn prior to vaccinations.
† Routine pediatric vaccines recommended at this age are to be given as per standard of care, and will not be provided by the Sponsor.
‡Blood sample at Visit 2 is applicable only to approximately the first 50% of the subjects in Group 1 and Group 2.
§Blood sample at Visit 3 is applicable only to the subjects in Group 1 and Group 2 who did not provide a blood sample at Visit 2 (approximately 50% in each group).
** PCV13 and Hib may be given as per standard of care outside of the study during the last study visit after completing all the study procedures (Visit 4). PCV13 and Hib will not be provided by the Sponsor.

Table 2: Vaccination and blood sampling schedule - Group 3 and Group 4

Age in months	**17-19 months**		**20-23 months**	**21-24 months**
Visit #	Visit 1		Visit 2	Visit 3
Procedure	**Blood Draw***	**Vaccine**	**Vaccine**	**Blood Draw**
Group 3	X	MenACYW	MenACYW	X
Group 4	X	Menactra	Menactra	X

*Blood will be drawn prior to vaccinations.

Objective

The primary objective was to demonstrate the non-inferiority (NI) of the vaccine seroresponse to meningococcal serogroups A, C, Y, and W following administration of 2 doses of MenACYW conjugate

vaccine compared to 2 doses of MENVEO when given concomitantly with routine paediatric vaccines to infants and toddlers 6 to 7 months of age and 12 to 13 months of age.

The secondary objectives were:

- To demonstrate the NI of the percentage of subjects with serum bactericidal assay using human complement (hSBA) titres to meningococcal serogroups A, C, Y, and W ≥ 1:8 following administration of 2 doses of MenACYW conjugate vaccine compared to 2 doses of MENVEO when given concomitantly with paediatric routine vaccines to infants and toddlers at 6 to 7 months of age and 12 to 13 months of age;
- To describe the antibody response against meningococcal serogroups A, C, Y, and W 30 days after the second vaccination at 12 to 13 months of age with MenACYW conjugate vaccine or MENVEO;
- To describe the antibody response against meningococcal serogroups A, C, Y, and W 30 days after the first vaccination at 6 to 7 months of age with MenACYW conjugate vaccine or MENVEO (in a subset of subjects);
- To describe the antibody response against meningococcal serogroups A, C, Y, and W 6 months after the first vaccination at 6 to 7 months of age with MenACYW conjugate vaccine or MENVEO (in a subset of subjects);
- To describe the antibody response against meningococcal serogroups A, C, Y, and W 30 days after the second vaccination at 20 to 23 months of age with MenACYW conjugate vaccine or Menactra.

The observational safety objectives were:

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

Outcomes/endpoints

Primary endpoint

The primary endpoint for the evaluation of immunogenicity was meningococcal serogroups A, C, Y, and W antibody titres measured by hSBA, before the first study vaccination (Visit 1) and 30 days after the second dose of MenACYW conjugate vaccine or MENVEO (Group 1 vs Group 2).

Secondary endpoints

The following serological endpoints were assessed:

1. Meningococcal serogroups A, C, Y, and W antibody titres ≥1:8 measured by hSBA 30 days after the second dose of MenACYW conjugate vaccine or MENVEO (Group 1 vs Group 2).
2. 30 days after the second vaccination at 12 to 13 months of age with MenACYW conjugate vaccine or MENVEO (Group 1 and Group 2):
    - hSBA meningococcal serogroups A, C, Y, and W antibody titres;
    - Geometric mean titres (GMTs) with 95% confidence interval (CI);
    - Titre distribution and reverse cumulative distribution curves (RCDCs);

- Percentage of subjects with titre ≥ 4-fold rise from pre-vaccination to post-vaccination and 95% CI.

3. 30 days after the first vaccination at 6 to 7 months of age with MenACYW conjugate vaccine or MENVEO (Group 1 and Group 2):
   - hSBA meningococcal serogroups A, C, Y, and W antibody titres;
   - GMTs with 95% CI;
   - titre distribution and RCDCs;
   - Percentage of subjects with titre ≥ 4-fold rise from pre-vaccination to post-vaccination and 95% CI;
   - Percentage of subjects with hSBA vaccine seroresponse and 95% CI.
4. 6 months after the first vaccination at 6 to 7 months of age (pre-vaccination 2) with MenACYW conjugate vaccine or MENVEO (Group 1 and Group 2):
   - hSBA meningococcal serogroups A, C, Y, and W antibody titres;
   - GMTs with 95% CI;
   - titre distribution and RCDCs;
   - Percentage of subjects with titre ≥ 4-fold rise from pre-vaccination to post-vaccination and 95% CI;
   - Percentage of subjects with hSBA vaccine seroresponse and 95% CI.
5. 30 days after the second vaccination at 20 to 23 months of age with MenACYW conjugate vaccine or Menactra (Group 3 and Group 4):
   - hSBA meningococcal serogroups A, C, Y, and W antibody titres;
   - GMTs with 95% CI;
   - titre distribution and RCDCs;
   - Percentage of subjects with titre ≥ 4-fold rise from pre-vaccination to post-vaccination and 95% CI;
   - Percentage of subjects with hSBA vaccine seroresponse and 95% CI.

Safety endpoints:

Safety endpoints and time windows are summarized in the table below. Further details on the criteria for analysis of safety, definitions, and the analysis populations were provided in the MET61 CSR.

Table 3: Safety endpoints

Safety Parameter	Data Collected and Collection Window
Immediate Unsolicited adverse events (AEs)/adverse reactions* (ARs)	0-30 minutes after vaccination by System Organ Class (SOC) and preferred term (PT)
Solicited (pre-defined) Injection Site Reactions	Within 7 days after vaccination by time of onset, number of days of occurrence, and maximum intensity
Solicited (pre-defined) Systemic Reactions	Within 7 days after vaccination by time of onset, number of days of occurrence, and maximum intensity
Unsolicited non-serious AEs/ARs	Within 30 days after vaccination by SOC and PT, time of onset, duration, and maximum intensity
Adverse Events of Special Interest (AESIs)	All AESIs were collected throughout the trial as SAEs to ensure that the events are communicated to the Sponsor in an expedited manner and followed up until the end of the follow-up period or resolution, as per the assigned causality
Serious Adverse Events (SAEs): All and related	SAEs were collected throughout the trial ensure that the events are communicated to the Sponsor in an expedited manner and followed up until the end of the follow-up period or resolution, as per the assigned causality
Deaths	Occurring throughout the trial period
Medically-attended adverse events (MAAEs)	MAAEs were collected throughout the trial from Visit 1 up to the 6-month follow-up contact after the last vaccination

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

Sample size

Approximately 870 subjects were to be enrolled in Group 1 and Group 2. An estimated 20% to 30% and not higher than 40% of non-evaluable subjects was to result in at least 522 subjects in the Per-Protocol population available for immunogenicity analyses. Group 1 was to have 435 enrolled subjects and 261 evaluable subjects. Group 2 was to have 435 enrolled subjects and 261 evaluable subjects. In addition, 200 subjects were to be enrolled in Group 3 and Group 4.

Primary Objective: Thirty days after the month 12 vaccination (after the second dose vaccination)

With at least 261 evaluable subjects in Group 1 and at least 261 evaluable subjects in Group 2, the study was to have around 90.0% power by using Farrington and Manning's method to declare the non-inferiority of Group 1 vs Group 2.

Table 4: Power estimates to reject primary null hypothesis

Antigen	Endpoint	Estimated response (%)*	Non-inferiority margin	Power (%)
A	Seroresponse Rate	97.7	10%	100
C	Seroresponse Rate	97.8	10%	100
Y	Seroresponse Rate	93.3	10%	99.0
W	Seroresponse Rate	86.7	10%	91.0
Overall				90.0

Note: Evaluable subjects: Group 1 = 261 subjects; Group 2 = 261 subjects
*Estimated responses were based on results observed in MET39

Secondary Objective: Thirty days after the month 12 vaccination (after the second dose vaccination)

With 261 evaluable subjects in Group 1 and 261 evaluable subjects in Group 2, the study was to have 100% power by using Farrington and Manning's method to declare the non-inferiority of Group 1 vs Group 2.

Table 5: Power estimates to reject the secondary null hypothesis

Antigen	Endpoint	Estimated response (%)*	Non-inferiority margin	Power (%)
A	% ≥1:8	>99.9	10%	100
C	% ≥1:8	>99.9	10%	100
Y	% ≥1:8	97.8	10%	100
W	% ≥1:8	97.8	10%	100
Overall				100

Note: Evaluable subjects: Group 1 = 261 subjects; Group 2 = 261 subjects
*Estimated responses were based on results observed in MET39

Randomisation and blinding (masking)

Randomisation

On the day of enrolment, subjects who meet the inclusion/exclusion criteria and whose parent / guardian signs the ICF will be randomly assigned to either Groups 1, 2 or Groups 3, 4 in a 1:1 ratio depending on the age at recruitment. Approximately 870 healthy infants 6 to7 months of age will be randomized 1:1 to either Group 1 or Group 2, and 200 healthy toddlers 17 to 19 months of age will be randomized 1:1 to either Group 3 or Group 4.

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 group assignment and have the site staff confirm it. 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 randomization codes will be kept securely in the IRT system.

Blinding

Given that the meningococcal vaccines (investigational and control) used in this study had different appearances, preparation methods, and vaccination schedules, the study had a modified double blind design for each group at enrolment, i.e., modified double-blind between Group 1 and Group 2, and between Group 3 and Group 4, and thus, with the exception of the personnel administering the vaccine, everyone involved in study (participants, care provider, investigator, safety outcomes assessor, Sponsor) was blinded to avoid any bias.

The code was permitted to 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 was to be limited to the subject(s) experiencing the AE.

The blind could 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 was addressed by the site, the Investigator or a delegate was obligated to notify the Sanofi Pasteur RMO if a subject's code was broken. All contact attempts with the Sponsor prior to unblinding were to be documented in the source documents, and the code breaking CRF was to be completed.

A request for the code to be broken could also be made by the GPV Department through an internal system for reporting to Health authorities in the case of an SAE as described in 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.

Statistical Methods

Primary objective

Thirty days after receiving MenACYW conjugate vaccine at 12 months of age, the hSBA vaccine seroresponse rates against meningococcal serogroups A, C, Y, and W in Group 1 were non- inferior to the corresponding hSBA vaccine seroresponse rates against meningococcal serogroups A, C, Y, and W in Group 2. hSBA vaccine seroresponse for serogroups A, C, Y and W was defined as: For a subject with a pre-vaccination titre < 1:8, the post-vaccination titre should be ≥ 1:16; For a subject with a pre-vaccination titre ≥ 1:8, the post-vaccination titre should be ≥ 4-fold greater than the pre-vaccination titre.

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

where p(men, G1) and p(men, G2) were the percentages of subjects who achieved hSBA vaccine seroresponse in Group 1 and Group 2, respectively. Each of the serogroups A, C, Y, and W was tested separately. Assuming the difference between the 2 proportions was normally distributed, if the lower limit of the 2-sided 95% confidence interval (CI) of the difference between the 2 proportions was > -10%, the inferiority assumption was rejected. For the non-inferiority hypotheses using the seroresponse rates, the CI of the difference in proportions was computed using the Wilson Score method without continuity correction.

Secondary objective

Thirty days after receiving MenACYW conjugate vaccine at 12 months of age, the hSBA vaccine seroprotection rates against meningococcal serogroups A, C, Y, and W in Group 1 was noninferior to the corresponding hSBA vaccine seroprotection rates against meningococcal serogroups A, C, Y, and W in Group 2.

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

where p(men, G1) and p(men, G2) were the percentages of subjects who achieved hSBA vaccine seroprotection (hSBA vaccine seroprotection for serogroups A, C, Y and W was defined as titres ≥ 1:8***)*** in Group 1 and Group 2, respectively. Each of the serogroups A, C, Y, and W were tested separately. Assuming the difference between the 2 proportions was normally distributed, if the lower limit of the 2-sided 95% CI of the difference between the 2 proportions was > -10%, the inferiority assumption was rejected. The CI of the difference in proportions was computed using the Wilson Score method without continuity correction.

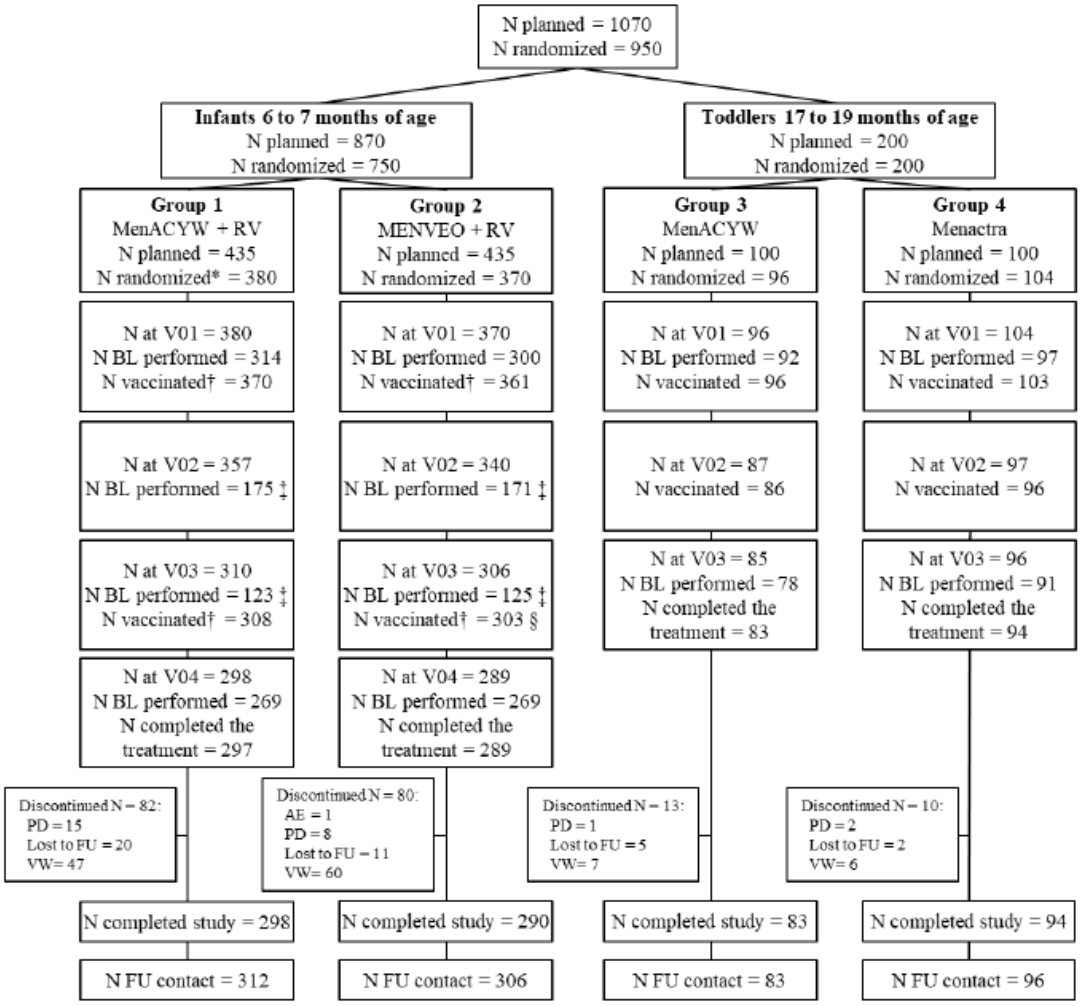
In general, categorical variables were summarized and presented by frequency counts, proportion percentages, and CIs. The 95% CIs of point estimates were calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for proportions. For GMTs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

Results

Participant flow

A total of 950 participants were enrolled and randomized in the study: 380 participants were randomized to Group 1, 370 were randomized to Group 2, 96 were randomized to Group 3, and 104 were randomized to Group 4. A total of 298 (78.4%) in group 1, 290 (78.4%) in group 2, 83 (86.5%) in group 3, and 94 (90,4%) in group 4 completed the study. A subject disposition flow chart and a tabular summary of disposition/vaccine allocation for randomised subjects are presented below.

Figure 1: Participant disposition flow chart



Abbreviations: BL, blood sample, FU, follow-up; PD, protocol deviation; RV, routine vaccines; V, visit; VW, voluntary parental/LAR withdrawal

* One participant was randomized with a wrong date of birth (at 18 months of age instead of 6-7 months of age) and did not receive any study intervention

†N vaccinated for MenACYW conjugate vaccine (Group 1) or MENVEO® (Group 2); participants received concomitant routine vaccines at Visit 1 (DTaP, IPV, Hib, PCV13, Rotavirus, Hepatitis B) and at Visit 2 (MMR and varicella); participants in Groups 1 and 2 received only routine vaccines at Visit 4 (PCV13 + Hib)

‡ Blood sample was applicable at Visit 2 to the first 50% of the participants in Groups 1 and 2 and at Visit 3 only to the participants in Groups 1 and 2 who did not provide a blood sample at Visit 2

§ One participant in Group 2 received the wrong vaccination during this visit (ie, received MenACYW conjugate vaccine instead of MENVEO®)

The number of enrolled participants was lower than planned and the number of participants who discontinued the study due to parent withdrawal was higher than expected due to COVID-19 pandemic conditions when parents were not ready to come or to return to research sites.

Table 6: Disposition by randomized group - Randomized Study participants

	Vaccination in infancy		Vaccination in the 2nd year of life	
	Group 1	**Group 2**	**Group 3**	**Group 4**
Visit 1	*At 6-7 months of age*		*At 17-19 months of age*	
Present at visit	380 (100%)	370 (100%)	96 (100%)	104 (100%)
Provided a blood sample	314 (82.6%)	300 (81.1%)	92 (95.8%)	97 (93.3%)
Received MenACYW conjugate vaccine or MENVEO® or Menactra®	370 (97.4%)	361 (97.6%)	96 (100%)	103 (99.0%)
Received Pentacel	218 (57.4%)	215 (58.1%)	-	-
Received ENGERIX-B or Recombivax HB	217 (57.1%)	213 (57.6%)	-	-
Received Pediarix	151 (39.7%)	146 (39.5%)	-	-
Received ActHib, Hiberix or PedvaxHIB	136 (35.8%)	137 (37.0%)	-	-
Received Prevnar 13	370 (97.4%)	360 (97.3%)	-	-
Received RotaTeq	370 (97.4%)	358 (96.8%)	-	-
Visit 2	*At 7-8 months of age*		*At 20-23 months of age*	
Present at visit	357 (93.9%)	340 (91.9%)	87 (90.6%)	97 (93.3%)
Provided a blood sample*	175 (46.1%)	171 (46.2%)	-	-
Received MenACYW conjugate vaccine or Menactra®	-	-	86 (89.6%)	96 (92.3%)
Visit 3	*At 12 months of age*		*At 21-24 months of age*	
Present at visit	310 (81.6%)	306 (82.7%)	85 (88.5%)	96 (92.3%)
Provided a blood sample**	123 (32.4%)	125 (33.8%)	78 (81.3%)	91 (87.5%)
Received MenACYW or MENVEO®	308 (81.1%)	302 (81.6%)§	-	-
Received M-M-R-II	306 (80.5%)	298 (80.5%)	-	-
Received Varivax	306 (80.5%)	298 (80.5%)	-	-
Visit 4	*At 13 months of age*			
Present at visit	298 (78.4%)	289 (78.1%)		
Provided a blood sample	269 (70.8%)	269 (72.7%)		

*Blood sample at Visit 2 is applicable to the first 50% of the participants in Group 1 and Group 2
**Blood sample at Visit 3 is applicable to the participants in Group 1 and Group 2 who did not provide a blood sample at Visit 2 (50% of participants in each group)
§ One participant (0.3%) in Group 2 received MenACYW conjugate vaccine
Group 1: MenACYW conjugate vaccine + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Group 2: MENVEO® + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Group 3: MenACYW conjugate vaccine at 17 to 19 months of age and 20 to 23 months of age
Group 4: Menactra® at 17 to 19 months of age and 20 to 23 months of age

Recruitment

This study was conducted at 47 centres that enrolled and randomized subjects in United States and Puerto Rico.

- Study initiation date (first subject first visit): 04 October 2018
- Study completion date (last subject last contact): 23 October 2023
- Database lock: 08 January 2024

Baseline data

A summary of baseline demographics for all randomised subjects is presented in the table below. There were more males than females in Group 1 (200 [52.6%] males and 180 [47.4%] females), and in Group 2 (198 [53.5%] males and 172 [46.5%] females). The percentage of males and females was balanced in Group 3 (48 [50.0%] males and 48 [50.0%] females), and in Group 4 (52 [50.0%] males

and 52 [50.0%] females). The male/female ratio was 1.11 in Group 1, 1.15 in Group 2, 1.00 in Group 3, and 1.00 in Group 4. The mean age (± standard deviation [SD]) of participants at enrolment was 6.01 (± 0.700) months in Group 1, 6.02 (± 0.396) months in Group 2, 17.9 (± 0.632) months in Group 3, and 17.9 (± 0.673) in Group 4.

Table 7: Baseline demographic by randomized group - Randomized Study participants

	Group 1 (N=380)	Group 2 (N=370)	Group 1 +Group 2 (N=750)	Group 3 (N=96)	Group 4 (N=104)	Group 3 +Group 4 (N=200)
Sex: n (%)						
Male	200 (52.6)	198 (53.5)	398 (53.1)	48 (50.0)	52 (50.0)	100 (50.0)
Female	180 (47.4)	172 (46.5)	352 (46.9)	48 (50.0)	52 (50.0)	100 (50.0)
Sex ratio: Male/Female	1.11	1.15	1.13	1.00	1.00	1.00
Age: (Months)						
M	379	370	749	96	104	200
Mean (SD)	6.01 (0.700)	6.02 (0.396)	6.01 (0.570)	17.9 (0.632)	17.9 (0.673)	17.9 (0.652)
Min ; Max	5.00 ; 18.0*	5.00 ; 7.00	5.00 ; 18.0	17.0 ; 19.0	17.0 ; 19.0	17.0 ; 19.0
Median	6.00	6.00	6.00	18.0	18.0	18.0
Q1 ; Q3	6.00 ; 6.00	6.00 ; 6.00	6.00 ; 6.00	17.0 ; 18.0	17.0 ; 18.0	17.0 ; 18.0
Racial origin: n (%)						
American Indian or Alaska Native	0	1 (0.3)	1 (0.1)	0	0	0
Asian	6 (1.6)	6 (1.6)	12 (1.6)	2 (2.1)	1 (1.0)	3 (1.5)
Black or African American	70 (18.4)	68 (18.4)	138 (18.4)	11 (11.5)	11 (10.6)	22 (11.0)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
White	277 (72.9)	264 (71.4)	541 (72.1)	79 (82.3)	87 (83.7)	166 (83.0)
Mixed origin	14 (3.7)	20 (5.4)	34 (4.5)	4 (4.2)	5 (4.8)	9 (4.5)
Not Reported	10 (2.6)	4 (1.1)	14 (1.9)	0	0	0
Unknown	3 (0.8)	7 (1.9)	10 (1.3)	0	0	0
Ethnicity: n (%)						
Hispanic or Latino	169 (44.5)	161 (43.5)	330 (44.0)	31 (32.3)	35 (33.7)	66 (33.0)
Not-Hispanic or Latino	208 (54.7)	209 (56.5)	417 (55.6)	65 (67.7)	69 (66.3)	134 (67.0)

	Group 1 (N=380)	Group 2 (N=370)	Group 1 +Group 2 (N=750)	Group 3 (N=96)	Group 4 (N=104)	Group 3 +Group 4 (N=200)
Not Reported	2 (0.5)	0	2 (0.3)	0	0	0
Unknown	1 (0.3)	0	1 (0.1)	0	0	0

n: number of participants fulfilling the item listed in the first column
N: number of participants randomized in each study group; Percentages are based on N
Q1; Q3: first quartile; third quartile; SD: Standard Deviation
Group 1: MenACYW conjugate vaccine + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Group 2: MENVEO® + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Group 3: MenACYW conjugate vaccine at 17 to 19 months of age and 20 to 23 months of age
Group 4: Menactra® at 17 to 19 months of age and 20 to 23 months of age
*One participant was randomized with a wrong date of birth (at 17 months of age instead of 7 months of age) and did not receive any study intervention

Numbers analysed

Definition of the analysis sets:

- Overall SafAS: subjects who received at least 1 dose of the study vaccines and had any safety data available. All subjects had their safety analysed after any dose according to the vaccine received at the first dose. Safety data recorded for a vaccine received out of the protocol design were excluded from the analysis (and listed separately).
- SafAS1: subjects who had received the study vaccine at Visit 1 (Groups 1 and 2) around 6-7 months of age and had any safety data available. All subjects had their safety analysed after the Visit 1 dose according to the vaccines they received at Visit 1. Safety data recorded for a vaccine received out of the protocol design at Visit 1 were excluded from the analysis (and listed separately).

- SafAS2: subjects who had received the study vaccine at 12-13 months of age in Groups 1 and 2 at Visit 3 and had any safety data available. All subjects had their safety analysed after this dose according to the vaccines they received at that visit. Safety data recorded for a vaccine received out of the protocol design at that Visit 3 were excluded from the analysis (and listed separately).
- SafAS3: subjects who had received the study vaccine at Visit 1 at 17-19 months of age in Groups 3 and 4 and had any safety data available. All subjects had their safety analysed after this dose according to the vaccines they received at that visit. Safety data recorded for a vaccine received out of the protocol design at that Visit 1 (Groups 3 and 4) were excluded from the analysis (and listed separately).
- SafAS4: subjects who had received the study vaccine at Visit 2 (Groups 3 and 4) at 20-23 months of age and had any safety data available. All subjects had their safety analysed after this dose according to the vaccine they received at that visit. Safety data recorded for a vaccine received out of the protocol design at that Visit 2 were excluded from the analysis (and listed separately).
- FAS1: subset of all randomized subjects who received ≥ 1 dose of the study vaccine in infancy (< 12 months of age) and had a valid post vaccination serology result in infancy. All subjects were analysed according to the treatment group to which they were randomized.
- FAS2: subset of all randomized subjects who received ≥ 1 dose of the study vaccine in the second year of life (≥ 12 months of age) and had a valid post-vaccination serology result in the second year of life. All subjects were analysed according to the treatment group to which they were randomized.
- FAS3: subset of all randomized subjects who received ≥ 1 dose of the study vaccine in infancy (< 12 months of age) and had a valid pre-vaccination serology result at Visit 3. All subjects were analysed according to the treatment group to which they were randomized.
- PPAS1: subset of FAS1 subjects with a valid serology obtained 30 days after the vaccination visit at 6 to 7 months of age (post-vaccination 1) for all antigens and with no relevant protocol deviations.
- PPAS2: subset of FAS2 with a valid serology obtained 30 days after vaccination during the second year of life and with no relevant protocol deviations.
- PPAS3: subset of FAS3 with a valid serology obtained at Visit 3 (pre-vaccination 2) for persistence 6 months after infant vaccination and with no relevant protocol deviations.

Table 8: Study MET61 sample size

	Subjects aged 6-7 months of age, n		Subjects aged 17-19 months of age, n		Total subjects, n
	Group 1 (MenACYW conjugate vaccine + RV)	Group 2 (MENVEO + RV)	Group 3 (MenACYW conjugate vaccine)	Group 4 (Menactra)	
Planned	435	435	100	100	1070
Actual	380	370	96	104	950
Overall SafAS	370	361	96	103	930
SafAS1	370	361	-	-	731
SafAS2	309*	302	-	-	611
SafAS3	-	-	96	103	199
SafAS4	-	-	86	96	182
FAS1†	165	165	-	-	330
PPAS1	135	138	-	-	273
FAS2	257	259	76	90	682
PPAS2	180	163	61	65	469
FAS3†	122	120	-	-	242
PPAS3	108	96	-	-	204

Abbreviations: FAS, Full Analysis Set; PPAS, Per-protocol Analysis Set; RV, routine vaccines; SafAS: Safety Analysis Set; n, number of study subjects fulfilling the item listed

* 1 subject randomized in Group 2 received MenACYW conjugate vaccine at Visit 3

†Subset of subjects assigned to blood sampling at Visit 2 for the FAS1 and at Visit 3 for the FAS3

Exposure

Out of 950 randomized participants (750 participants in Group 1 + Group 2 and 200 participants in Group 3 + Group 4), a total of 930 participants received at least one dose of study vaccine and were included in the Overall Safety Analysis after any dose: 370 participants in Group 1, 361 participants in Group 2, 96 participants in Group 3, and 103 participants in Group 4. There were 19 participants in Group 1 + Group 2 and 1 participant in Group 3 + Group 4 who were randomized but not vaccinated.

Table 9: Exposure

	Vaccination in infancy, n (%)		Vaccination in the 2nd year of life, n (%)	
	Group 1	**Group 2**	**Group 3**	**Group 4**
Visit 1	***At 6-7 months of age***		***At 17-19 months of age***	
Present at visit	380 (100%)	370 (100%)	96 (100%)	104 (100%)
Provided a blood sample	314 (82.6%)	300 (81.1%)	92 (95.8%)	97 (93.3%)
Received MenACYW conjugate vaccine or MENVEO or Menactra	370 (97.4%)	361 (97.6%)	96 (100%)	103 (99.0%)
Received Pentacel	218 (57.4%)	215 (58.1%)	-	-
Received ENGERIX-B or Recombivax HB	217 (57.1%)	213 (57.6%)	-	-
Received Pediarix	151 (39.7%)	146 (39.5%)	-	-
Received ActHib, Hiberix or PedvaxHIB	136 (35.8%)	137 (37.0%)	-	-
Received Prevnar 13	370 (97.4%)	360 (97.3%)	-	-
Received RotaTeq	370 (97.4%)	358 (96.8%)	-	-
Visit 2	***At 7-8 months of age***		***At 20-23 months of age***	
Present at visit	357 (93.9%)	340 (91.9%)	87 (90.6%)	97 (93.3%)
Provided a blood sample*	175 (46.1%)	171 (46.2%)	-	-
Received MenACYW conjugate vaccine or Menactra	-	-	86 (89.6%)	96 (92.3%)
Visit 3	***At 12-13 months of age***		***At 21-24 months of age***	
Present at visit	310 (81.6%)	306 (82.7%)	85 (88.5%)	96 (92.3%)
Provided a blood sample*	123 (32.4%)	125 (33.8%)	78 (81.3%)	91 (87.5%)
Received MenACYW conjugate vaccine or MENVEO	308 (81.1%)	302 (81.6%)†	-	-
Received M-M-R-II	306 (80.5%)	298 (80.5%)	-	-
Received Varivax	306 (80.5%)	298 (80.5%)	-	-
Visit 4	***At 13-14 months of age***			
Present at visit	298 (78.4%)	289 (78.1%)		
Provided a blood sample	269 (70.8%)	269 (72.7%)		

*For Groups 1 and 2: subset of subjects (approximately 50% of the subjects in Groups 1 and 2)
† In addition, 1 subject (0.3%) in Group 2 received MenACYW conjugate vaccine

Study discontinuation

The discontinuation rate during the study was high. Of the 950 subjects enrolled and randomized, only 765 (80.5%) completed the study: 298 (78.4%) subjects in Group 1, 290 (78.4%) subjects in Group 2, 83 (86.5%) subjects in Group 3, and 94 (90.4%) subjects in Group 4. The reasons for discontinuation are shown in the table below.

Table 10: Study subjects with early termination by randomized group - Randomized Study subjects

	Group 1 (N=380) n (%)	Group 2 (N=370) n (%)	Group 3 (N=96) n (%)	Group 4 (N=104) n (%)	All (N=950) n (%)
Completed	298 (78.4)	290 (78.4)	83 (86.5)	94 (90.4)	765 (80.5)
Early termination	82 (21.6)	80 (21.6)	13 (13.5)	10 (9.6)	185 (19.5)
Reason					
Adverse Event	0	1 (0.3)	0	0	1 (0.1)
Protocol Deviation	15 (3.9)	8 (2.2)	1 (1.0)	2 (1.9)	26 (2.7)
Withdrawal by Parent/Guardian	47 (12.4)	60 (16.2)	7 (7.3)	6 (5.8)	120 (12.6)
Lost to Follow-Up	20 (5.3)	11 (3.0)	5 (5.2)	2 (1.9)	38 (4.0)

This high discontinuation rate was due to high parental/LAR withdrawal rate. The main reasons for the parental/LAR withdrawals were not specified (no reasons were provided) or were motivated by concerns regarding blood sampling (number of blood sampling during the study and/or after one or

more unsuccessful blood sampling attempts), or were related to the fact that the parents finally choose regular vaccines, or to reasons relative to the COVID-19 pandemic situation and its impact on people's mobility as some parents were unable to come to research sites. Less than 10% of subjects were directly impacted by the COVID-19 pandemic situation.

Study conduct

Protocol deviations

Table 11: Major and critical protocol deviations by randomized group - Randomized Study Subjects

	Group 1 (N=380) n (%)	Group 2 (N=370) n (%)	Group 3 (N=96) n (%)	Group 4 (N=104) n (%)	All (N=950) n (%)
Subjects with at least one major or critical protocol deviation	258 (67.9)	256 (69.2)	42 (43.8)	44 (42.3)	600 (63.2)
Subjects with at least one major protocol deviation	258 (67.9)	256 (69.2)	42 (43.8)	44 (42.3)	600 (63.2)
Informed consent not obtained for an amendment requiring a reconsent	3 (0.8)	4 (1.1)	0	0	7 (0.7)
Informed consent obtained with an error in consent process or documentation	1 (0.3)	1 (0.3)	1 (1.0)	1 (1.0)	4 (0.4)
Born at full term of pregnancy (less than or equal to 37 weeks) and with a birth weight greater than or equal to 2.5 kg	2 (0.5)	2 (0.5)	1 (1.0)	0	5 (0.5)
Subject and parent/guardian are able to attend all scheduled visits and to comply with all trial procedures	1 (0.3)	0	0	0	1 (0.1)
For subjects to be enrolled at 6 to 7 months of age (Group 1 and Group 2), documented history of having received 2 doses of DTaP, Hib, IPV, pneumococcal, hepatitis B (for children who received Pediarix at 2 and 4 months of age, prior receipt of 3 doses of hepatitis B), and rotavirus (Rotateq) vaccines	6 (1.6)	2 (0.5)	0	0	8 (0.8)
For subjects to be enrolled at 17 to 19 months of age (Group 3 and Group 4), documented history of having received all routine pediatric vaccines recommended by ACIP up to the age of enrollment	0	0	8 (8.3)	11 (10.6)	19 (2.0)
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	0	1 (0.3)	0	0	1 (0.1)
Receipt of any vaccine in the 4 weeks preceding the first trial vaccination or planned receipt of any vaccine in the 4 weeks before and / or following any trial vaccination except for influenza vaccination, which may be received at least 2 weeks before or 2 weeks after any study vaccination. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines	2 (0.5)	2 (0.5)	3 (3.1)	3 (2.9)	10 (1.1)
Previous vaccination against meningococcal disease with either the trial vaccine or another vaccine (i.e., mono- or polyvalent, PS, or conjugate meningococcal vaccine containing serogroups A, C, Y, or W; or meningococcal B serogroup-containing vaccine)	0	1 (0.3)	0	0	1 (0.1)
For subjects to be enrolled at 6 to 7 months of age (Group 1 and Group 2), prior receipt of more than 2 doses of rotavirus vaccine (Rotateq), DTaP, Hib, IPV, pneumococcal, hepatitis B; for children who received Pediarix at 2 and 4 months of age, prior receipt of more than 3 doses of hepatitis B vaccine	3 (0.8)	1 (0.3)	0	0	4 (0.4)
For subjects to be enrolled at 6 to 7 months of age (Group 1 and Group 2), receipt of the rotavirus vaccine, Rotarix at 2 and 4 months of age	5 (1.3)	2 (0.5)	0	0	7 (0.7)
Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw	0	1 (0.3)	0	0	1 (0.1)
Protocol-specified co-administered routine vaccine not received	75 (19.7)	69 (18.6)	0	0	144 (15.2)
Protocol specified routine vaccine was administered but not within the protocol-specified time window	52 (13.7)	48 (13.0)	1 (1.0)	0	101 (10.6)
Protocol prohibited therapy/medication/vaccine received	7 (1.8)	8 (2.2)	2 (2.1)	11 (10.6)	28 (2.9)
Protocol-specified routine vaccine was administered but not as per protocol	2 (0.5)	7 (1.9)	0	0	9 (0.9)
Subject received an unacceptable protocol specified co-administered routine vaccine for use	5 (1.3)	2 (0.5)	0	0	7 (0.7)
Study visit, telephone call or safety contact not performed	31 (8.2)	30 (8.1)	4 (4.2)	8 (7.7)	73 (7.7)
Study visit, telephone call or safety contact was not performed within the protocol-specified time window	57 (15.0)	64 (17.3)	9 (9.4)	10 (9.6)	140 (14.7)
Planned sample not performed	180 (47.4)	161 (43.5)	20 (20.8)	19 (18.3)	380 (40.0)
Planned sample not performed within the protocol-specified time window	70 (18.4)	71 (19.2)	6 (6.3)	10 (9.6)	157 (16.5)
Study procedure performed by unqualified / unauthorized personnel	4 (1.1)	6 (1.6)	0	1 (1.0)	11 (1.2)
Sample handled incorrectly during collection, processing, storage or shipment	9 (2.4)	6 (1.6)	1 (1.0)	0	16 (1.7)
IMP was not administered	71 (18.7)	62 (16.8)	10 (10.4)	8 (7.7)	151 (15.9)
IMP was administered but not as per protocol	1 (0.3)	1 (0.3)	0	0	2 (0.2)
IMP was administered but not within the protocol-specified time window	22 (5.8)	20 (5.4)	3 (3.1)	2 (1.9)	47 (4.9)
Subject received an unacceptable IMP for use	3 (0.8)	1 (0.3)	3 (3.1)	1 (1.0)	8 (0.8)
Not appropriate treatment blinding management by study staff	2 (0.5)	2 (0.5)	0	0	4 (0.4)
Randomization procedure not performed in the correct sequence as specified in the protocol	3 (0.8)	2 (0.5)	1 (1.0)	0	6 (0.6)
Subject randomized twice	0	1 (0.3)	0	0	1 (0.1)
IMP number actually given to the subject is different from the IMP number allocated by the randomization process	0	1 (0.3)	0	0	1 (0.1)
Other randomization error	1 (0.3)	1 (0.3)	0	0	2 (0.2)
Erroneous subject diary card given to the subject	0	1 (0.3)	0	0	1 (0.1)

	Group 1 (N=380) n (%)	Group 2 (N=370) n (%)	Group 3 (N=96) n (%)	Group 4 (N=104) n (%)	All (N=950) n (%)
Failure to report MAAE/AESI/SAE to sponsor within the protocol-specified time window (ex 24h for SAE and AESI)	2 (0.5)	4 (1.1)	1 (1.0)	1 (1.0)	8 (0.8)
Failure to complete AE/MAAE/AESI/SAE when information is available	2 (0.5)	1 (0.3)	0	0	3 (0.3)
30 minutes or immediate reaction post follow up not completed	3 (0.8)	1 (0.3)	0	0	4 (0.4)
Missing or not provided subject diary card	17 (4.5)	23 (6.2)	2 (2.1)	2 (1.9)	44 (4.6)
Failure to capture AE/AESI/SAE/MAAE	0	4 (1.1)	0	1 (1.0)	5 (0.5)
Inexistent, missing or incomplete source data	2 (0.5)	3 (0.8)	0	0	5 (0.5)
Other	0	1 (0.3)	0	0	1 (0.1)
Subjects with at least one critical protocol deviation	0	0	0	0	0

n: number of Subjects fulfilling the item listed

Group 1: MenACYW conjugate vaccine + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age

Group 2: MENVEO + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age

Group 3: MenACYW conjugate vaccine at 17 to 19 months of age and 20 to 23 months of age

Group 4: Menactra at 17 to 19 months of age and 20 to 23 months of age

Study: MET61 Program: t08016.sas Datasets=ADSL ADDV Output: PRODOPS/SP0047/MET61/CSR_01/REPORT/OUTPUT/T08016_i.rtf (08MAR2024 15:11)

One subject in Group 1 was randomized with a wrong date of birth (at 18 months of age instead of 6-7 months of age) and did not receive any study intervention

Efficacy results

Primary Immunogenicity Endpoint

The primary objective was to demonstrate the NI of the vaccine seroresponse rate to meningococcal serogroups A, C, Y, and W following sequential administration of 2 doses of MenACYW conjugate vaccine (Group 1) compared to 2 doses of MENVEO (Group 2) when given concomitantly with routine paediatric vaccines to infants and toddlers 6 to 7 months of age and 12 to 13 months of age.

The primary objective was met. At D30 after the second vaccination at 12 to 13 months of age, the NI of MenACYW conjugate vaccine (Group 1) compared to MENVEO (Group 2) was demonstrated in the PPAS2 as the lower limit of the 95% CI of the difference in the proportion of subjects with an hSBA seroresponse for meningococcal serogroups A, C, W, and Y was greater than -10%.

The NI of hSBA vaccine seroresponse rate 30 days after the second dose of MenACYW conjugate vaccine (Group 1) or MENVEO (Group 2) in the PPAS2 is presented below. The NI was also demonstrated in the FAS2.

Table 12: Non-inferiority of hSBA vaccine seroresponse rate 30 days after the second dose of MenACYW conjugate vaccine or MENVEO (Group 1 vs Group 2) - Per-Protocol Analysis Set 2

	Group 1 (N=180)			Group 2 (N=163)			Group 1 minus Group 2		
Serogroup	n/M	%	(95% CI)	n/M	%	(95% CI)	Difference (%)	(95% CI)	Non-inferiority
A	126/141	89.4	(83.1 ; 93.9)	102/123	82.9	(75.1 ; 89.1)	6.43	(-1.92 ; 15.08)	Yes
C	133/134	99.3	(95.9 ; 100)	123/126	97.6	(93.2 ; 99.5)	1.63	(-2.07 ; 6.06)	Yes
Y	138/140	98.6	(94.9 ; 99.8)	125/128	97.7	(93.3 ; 99.5)	0.92	(-3.03 ; 5.36)	Yes
W	142/143	99.3	(96.2 ; 100)	118/127	92.9	(87.0 ; 96.7)	6.39	(1.81 ; 12.25)	Yes

n: number of participants who achieve an hSBA vaccine seroresponse; M: number of participants with available data for the relevant endpoint

N: number of participants in per-protocol analysis set for second year of life vaccination

95% CI of the single proportion calculated from the exact binomial method; 95% CI of the difference calculated from the Wilson Score method without continuity correction

hSBA vaccine seroresponse is defined as a post-vaccination titer ≥1:16 for participants with pre-vaccination hSBA titer < 1:8,

or a post-vaccination titer ≥4-fold increase from baseline for participant with pre-vaccination hSBA titer ≥1:8

The overall non-inferiority will be demonstrated if the lower limit of the 2-sided 95% CI is > -10% for all four serogroups.

Group 1: MenACYW conjugate vaccine + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age

Group 2: MENVEO® + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age

Table 13: Non-inferiority of hSBA vaccine seroresponse rate 30 days after the second dose of MenACYW conjugate vaccine or MENVEO (Group 1 vs Group 2) - Per-Protocol Analysis Set 2

	Group 1 (N=257)			Group 2 (N=259)			Group 1 minus Group 2		
Serogroup	n/M	%	(95% CI)	n/M	%	(95% CI)	Difference (%)	(95% CI)	Non-inferiority
A	175/196	89.3	(84.1 ; 93.2)	146/184	79.3	(72.8 ; 85.0)	9.94	(2.63 ; 17.30)	Yes
C	187/192	97.4	(94.0 ; 99.1)	184/192	95.8	(92.0 ; 98.2)	1.56	(-2.36 ; 5.68)	Yes
Y	191/199	96.0	(92.2 ; 98.2)	186/196	94.9	(90.8 ; 97.5)	1.08	(-3.29 ; 5.57)	Yes
W	195/201	97.0	(93.6 ; 98.9)	172/194	88.7	(83.3 ; 92.8)	8.36	(3.33 ; 13.83)	Yes

n: number of subjects who achieve an hSBA vaccine seroresponse; M: number of subjects with available data for the relevant endpoint.
N: number of subjects in full analysis set for second year of life vaccination
95% CI of the single proportion calculated from the exact binomial method
95% CI of the difference calculated from the Wilson Score method without continuity correction
The overall non-inferiority will be demonstrated if the lower limit of the 2-sided 95% CI is > -10% for all four serogroups.
Group 1: MenACYW conjugate vaccine + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Group 2: MENVEO + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Study: MET61 Program: t08176to179.sas Datasets=ADSL ADIS Output: PRODOPS/SP0047/MET61/CSR_01/REPORT/OUTPUT/T08177_i.rtf (08MAR2024 15:29)

Secondary immunogenicity endpoints

Secondary objective 1: Non-Inferiority of MenACYW Conjugate Vaccine Versus MENVEO Based on hSBA Titres ≥ 1:8 After 2 Doses (Groups 1 and 2)

The secondary objective 1 was to demonstrate the NI of the percentage of subjects with hSBA titres to meningococcal serogroups A, C, Y, and W ≥ 1:8 following administration of 2 doses of MenACYW conjugate vaccine (Group 1) compared to 2 doses of MENVEO (Group 2) when given concomitantly with paediatric routine vaccines to infants and toddlers at 6 to 7 months of age and 12 to 13 months of age.

Table 14: Non-inferiority of the percentage of subjects with hSBA titres >=1:8 - 30 days after the second dose of MenACYW conjugate vaccine

	Group 1 (N=180)			Group 2 (N=163)			Group 1 minus Group 2		
Serogroup	n/M	%	(95% CI)	n/M	%	(95% CI)	Difference (%)	(95% CI)	Non-inferiority
A	162/170	95.3	(90.9 ; 97.9)	147/158	93.0	(87.9 ; 96.5)	2.26	(-3.01 ; 7.83)	Yes
C	162/162	100	(97.7 ; 100)	157/160	98.1	(94.6 ; 99.6)	1.88	(-0.75 ; 5.37)	Yes
Y	170/170	100	(97.9 ; 100)	156/160	97.5	(93.7 ; 99.3)	2.50	(-0.18 ; 6.25)	Yes
W	171/171	100	(97.9 ; 100)	152/159	95.6	(91.1 ; 98.2)	4.40	(1.25 ; 8.81)	Yes

n: number of subjects who achieve an hSBA vaccine seroprotection; M: number of subjects with available data for the relevant endpoint.
N: number of subjects in per-protocol analysis set for second year of life vaccination
95% CI of the single proportion calculated from the exact binomial method;
95% CI of the difference calculated from the Wilson Score method without continuity correction
The overall non-inferiority will be demonstrated if the lower limit of the 2-sided 95% CI is > -10% for all four serogroups.
Group 1: MenACYW conjugate vaccine + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Group 2: MENVEO + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Study: MET61 Program: t08176to179.sas Datasets=ADSL ADIS Output: PRODOPS/SP0047/MET61/CSR_01/REPORT/OUTPUT/T08178_i.rtf (08MAR2024 15:29)

Secondary objective 2: Antibody Responses 30 Days After the Second Vaccination at 12 to 13 Months of Age With MenACYW conjugate Vaccine or MENVEO (Groups 1 and 2)

The secondary objective 2 was to describe the antibody response against meningococcal serogroups A, C, Y, and W 30 days after the second vaccination at 12 to 13 months of age with MenACYW conjugate vaccine (Group 1) or MENVEO (Group 2).

HSBA Antibody Titre ≥ 1:4 and ≥ 1:8

Table 15: Number and proportion of subjects with hSBA titre >= 1:4 and >= 1:8 at pre-dose 1 and 30 days after the second vaccination at 12 to 13 months of age - Per-Protocol Analysis Set 2

			Group 1 (N=180)			Group 2 (N=163)		
Serogroup	Time Point	hSBA Titers	n/M	%	(95% CI)	n/M	%	(95% CI)
A	D0 (Pre-Dose 1)	>=1:4	81/144	56.3	(47.7 ; 64.5)	65/127	51.2	(42.2 ; 60.1)
		>=1:8	42/144	29.2	(21.9 ; 37.3)	31/127	24.4	(17.2 ; 32.8)
	D30 (Post-Dose 2)	>=1:4	165/170	97.1	(93.3 ; 99.0)	150/158	94.9	(90.3 ; 97.8)
		>=1:8	162/170	95.3	(90.9 ; 97.9)	147/158	93.0	(87.9 ; 96.5)
C	D0 (Pre-Dose 1)	>=1:4	15/147	10.2	(5.8 ; 16.3)	16/129	12.4	(7.3 ; 19.4)
		>=1:8	9/147	6.1	(2.8 ; 11.3)	9/129	7.0	(3.2 ; 12.8)
	D30 (Post-Dose 2)	>=1:4	162/162	100	(97.7 ; 100)	159/160	99.4	(96.6 ; 100)
		>=1:8	162/162	100	(97.7 ; 100)	157/160	98.1	(94.6 ; 99.6)
Y	D0 (Pre-Dose 1)	>=1:4	23/149	15.4	(10.0 ; 22.3)	16/130	12.3	(7.2 ; 19.2)
		>=1:8	13/149	8.7	(4.7 ; 14.5)	8/130	6.2	(2.7 ; 11.8)
	D30 (Post-Dose 2)	>=1:4	170/170	100	(97.9 ; 100)	157/160	98.1	(94.6 ; 99.6)
		>=1:8	170/170	100	(97.9 ; 100)	156/160	97.5	(93.7 ; 99.3)
W	D0 (Pre-Dose 1)	>=1:4	10/148	6.8	(3.3 ; 12.1)	14/130	10.8	(6.0 ; 17.4)
		>=1:8	7/148	4.7	(1.9 ; 9.5)	8/130	6.2	(2.7 ; 11.8)
	D30 (Post-Dose 2)	>=1:4	171/171	100	(97.9 ; 100)	154/159	96.9	(92.8 ; 99.0)
		>=1:8	171/171	100	(97.9 ; 100)	152/159	95.6	(91.1 ; 98.2)

n: number of subjects experiencing the endpoint listed in the first 3 columns; M: number of subjects with available data for the relevant endpoint.
N: number of subjects in per-protocol analysis set 2
Group 1: MenACYW conjugate vaccine + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Group 2: MENVEO + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Study: MET61 Program: t08182n183.sas Datasets=ADIS ADSL Output: PRODOPS/SP0047/MET61/CSR_01/REPORT/OUTPUT/T08182_i.rtf (08MAR2024 15:29)

hSBA Meningococcal Serogroups A, C, Y, and W Antibody Titres

Table 16: Summary of geometric means of hSBA titres at pre-dose 1 and 30 days after the second vaccination at 12 to 13 months of age - Per-Protocol Analysis Set 2

			Group 1 (N=180)			Group 2 (N=163)	
Serogroup	Time Point	M	GMT	(95% CI)	M	GMT	(95% CI)
A	D0 (Pre-Dose 1)	144	4.73	(3.92 ; 5.72)	127	4.64	(3.74 ; 5.74)
	D30 (Post-Dose 2)	170	184	(143 ; 237)	158	119	(90.6 ; 157)
C	D0 (Pre-Dose 1)	147	2.57	(2.21 ; 2.99)	129	2.48	(2.20 ; 2.79)
	D30 (Post-Dose 2)	162	1473	(1236 ; 1756)	160	319	(263 ; 388)
Y	D0 (Pre-Dose 1)	149	2.54	(2.27 ; 2.83)	130	2.37	(2.16 ; 2.60)
	D30 (Post-Dose 2)	170	423	(358 ; 499)	160	133	(107 ; 166)
W	D0 (Pre-Dose 1)	148	2.23	(2.05 ; 2.42)	130	2.31	(2.13 ; 2.51)
	D30 (Post-Dose 2)	171	442	(367 ; 533)	159	106	(83.4 ; 135)

M: number of subjects with available data for the relevant endpoint
N: number of subjects in per-protocol analysis set 2
Group 1: MenACYW conjugate vaccine + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Group 2: MENVEO + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Study: MET61 Program: t08188n189n210n211.sas Datasets=ADSL ADIS Output: PRODOPS/SP0047/MET61/CSR_01/REPORT/OUTPUT/T08188_i.rtf (08MAR2024 15:30)

hSBA Antibody Titre ≥ 4-Fold Rise from Pre- to Post-vaccination

In the PPAS2, the percentages of participants with ≥ 4-fold rise of hSBA titre from pre-dose 1 to 30 days after the second vaccination at 12 to 13 months of age were comparable in both groups for serogroups C and Y and numerically higher in Group 1 as compared to Group 2 for serogroups A and W. The percentages of participants with a ≥ 4-fold rise of hSBA titre were:

- for serogroup A: 89.4% in Group 1 and 82.9% in Group 2
- for serogroup C: 99.3% in Group 1 and 97.6% in Group 2
- for serogroup Y: 98.6% in Group 1 and 97.7% in Group 2
- for serogroup W: 99.3% in Group 1 and 92.9% in Group 2

Secondary Objective 3: To describe the antibody response against meningococcal serogroups A, C, Y, and W 30 days after the first vaccination at 6 to 7 months of age with MenACYW conjugate vaccine or MENVEO

The secondary objective 3 was to describe the antibody response against meningococcal *s*erogroups A, C, Y, and W 30 days after the first vaccination at 6 to 7 months of age with MenACYW conjugate vaccine (Group 1) or MENVEO (Group 2).

hSBA Vaccine Seroresponse

Table *17*: Summary of subjects with hSBA vaccine seroresponse from pre-dose 1 to 30 days after the first vaccination at 6 to 7 months of age - Per-Protocol Analysis Set 1

		Group 1 (N=135)			Group 2 (N=138)		
Serogroup	Baseline status	n/M	%	(95% CI)	n/M	%	(95% CI)
A	Any	33/108	30.6	(22.1 ; 40.2)	17/111	15.3	(9.2 ; 23.4)
	S-	29/87	33.3	(23.6 ; 44.3)	15/88	17.0	(9.9 ; 26.6)
	S+	4/21	19.0	(5.4 ; 41.9)	2/23	8.7	(1.1 ; 28.0)
C	Any	96/104	92.3	(85.4 ; 96.6)	87/107	81.3	(72.6 ; 88.2)
	S-	92/97	94.8	(88.4 ; 98.3)	85/103	82.5	(73.8 ; 89.3)
	S+	4/7	57.1	(18.4 ; 90.1)	2/4	50.0	(6.8 ; 93.2)
Y	Any	31/102	30.4	(21.7 ; 40.3)	8/106	7.5	(3.3 ; 14.3)
	S-	30/93	32.3	(22.9 ; 42.7)	6/100	6.0	(2.2 ; 12.6)
	S+	1/9	11.1	(0.3 ; 48.2)	2/6	33.3	(4.3 ; 77.7)
W	Any	20/108	18.5	(11.7 ; 27.1)	9/112	8.0	(3.7 ; 14.7)
	S-	20/101	19.8	(12.5 ; 28.9)	7/103	6.8	(2.8 ; 13.5)
	S+	0/7	0	(0 ; 41.0)	2/9	22.2	(2.8 ; 60.0)

n: number of subjects achieving hSBA vaccine seroresponse criteria; M: number of subjects with available data for the relevant endpoint
N: number of subjects in per-protocol analysis set 1
hSBA vaccine seroresponse: titer is < 1:8 at baseline with post-vaccination titer >= 1:16 or titer is >= 1:8 at baseline with a >= 4-fold increase at post-vaccination
S-: Pre-vaccination baseline titer is < 1:8; S+: Pre-vaccination baseline titer is >= 1:8
Group 1: MenACYW conjugate vaccine + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Group 2: MENVEO + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Study: MET61 Program: t08204to207.sas Datasets=ADSL ADIS Output: PRODOPS/SP0047/MET61/CSR_01/REPORT/OUTPUT/T08204_i.rtf (08MAR2024 15:31)

hSBA Antibody Titre ≥ 1:4 and ≥ 1:8

In the PPAS1, at D30 after the first vaccination at 6 to 7 months of age, the percentages of subjects with meningococcal hSBA titres ≥ 1:4 and ≥ 1:8 were higher in Group 1 than in Group 2 for serogroup Y and numerically higher in Group 1 than in Group 2 for serogroups A, C, and W. The percentages of subjects with meningococcal hSBA titres ≥ 1:4 and ≥ 1:8 were:

- for serogroup A: 64.6% and 54.6% in Group 1 and 55.3% and 37.9% in Group 2
- for serogroup C: 96.9% and 96.9% in Group 1 and 93.2% and 90.2% in Group 2
- for serogroup Y: 70.4% and 60.8% in Group 1 and 43.0% and 26.6% in Group 2
- for serogroup W: 49.3% and 38.1% in Group 1 and 37.3% and 28.4% in Group 2

Meningococcal Serogroups A, C, Y, and W Antibody Titres

Table 18: Summary of geometric means of hSBA titres 30 days after the first vaccination at 6 to 7 months of age - Per-Protocol Analysis Set 1

	Group 1 (N=135)			Group 2 (N=138)		
Serogroup	M	GMT	(95% CI)	M	GMT	(95% CI)
A	130	8.26	(6.55 ; 10.4)	132	5.45	(4.42 ; 6.72)
C	127	167	(129 ; 217)	133	41.3	(32.8 ; 52.1)
Y	125	8.36	(6.61 ; 10.6)	128	3.79	(3.20 ; 4.49)
W	134	5.51	(4.39 ; 6.92)	134	3.82	(3.22 ; 4.52)

M: number of subjects with available data for the relevant endpoint
N: number of subjects in per-protocol analysis set 1
Group 1: MenACYW conjugate vaccine + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Group 2: MENVEO + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Study: MET61 Program: t08186n187n190n191.sas Datasets=ADSL ADIS Output: PRODOPS/SP0047/MET61/CSR_01/REPORT/OUTPUT/T08186_i.rtf (08MAR2024 15:29)

hSBA Antibody Titre ≥ 4-Fold Rise from Pre- to Post-vaccination

In the PPAS1, the percentages of subjects with ≥ 4-fold rise of hSBA titre from pre-dose 1 to 30 days after the first vaccination at 6 to 7 months of age were numerically higher in Group 1 than in Group 2 for serogroups A, C and W and was higher in Group 1 than in Group 2 for serogroup Y. The percentages of subjects with a ≥ 4-fold rise of hSBA titre were:

- for serogroup A: 30.6% in Group 1 and 15.3% in Group 2
- for serogroup C: 92.3% in Group 1 and 81.3% in Group 2
- for serogroup Y: 30.4% in Group 1 and 7.5% in Group 2
- for serogroup W: 18.5% in Group 1 and 8.0% in Group 2

Secondary Objective 4: Antibody Responses 6 Months After the First Vaccination at 6 to 7 Months of Age (pre-dose 2) With MenACYW Conjugate Vaccine or MENVEO (Groups 1 and 2)

The secondary objective 4 was to describe the antibody response against meningococcal serogroups A, C, Y, and W pre-dose 2 (6 months after the first vaccination at 6 to 7 months of age) with MenACYW conjugate vaccine (Group 1) or MENVEO (Group 2).

hSBA Vaccine Seroresponse

Table 19: Summary of subjects with hSBA vaccine seroresponse from pre-dose 2 to 30 days after the second vaccination at 12 to 13 months of age - Per-Protocol Analysis Set 2

		Group 1 (N=180)			Group 2 (N=163)		
Serogroup	Baseline status	n/M	%	(95% CI)	n/M	%	(95% CI)
A	Any	59/74	79.7	(68.8 ; 88.2)	58/70	82.9	(72.0 ; 90.8)
	S-	15/17	88.2	(63.6 ; 98.5)	16/18	88.9	(65.3 ; 98.6)
	S+	44/57	77.2	(64.2 ; 87.3)	42/52	80.8	(67.5 ; 90.4)
C	Any	69/74	93.2	(84.9 ; 97.8)	69/74	93.2	(84.9 ; 97.8)
	S-	1/1	100	(2.5 ; 100)	21/23	91.3	(72.0 ; 98.9)
	S+	68/73	93.2	(84.7 ; 97.7)	48/51	94.1	(83.8 ; 98.8)
Y	Any	64/74	86.5	(76.5 ; 93.3)	67/73	91.8	(83.0 ; 96.9)
	S-	4/4	100	(39.8 ; 100)	32/33	97.0	(84.2 ; 99.9)
	S+	60/70	85.7	(75.3 ; 92.9)	35/40	87.5	(73.2 ; 95.8)
W	Any	66/77	85.7	(75.9 ; 92.6)	68/73	93.2	(84.7 ; 97.7)
	S-	2/2	100	(15.8 ; 100)	33/36	91.7	(77.5 ; 98.2)
	S+	64/75	85.3	(75.3 ; 92.4)	35/37	94.6	(81.8 ; 99.3)

n: number of subjects achieving hSBA vaccine seroresponse criteria; M: number of subjects with available data for the relevant endpoint
N: number of subjects in per-protocol analysis set 2
hSBA vaccine seroresponse: titer is < 1:8 at baseline with post-vaccination titer >= 1:16 or titer is >= 1:8 at baseline with a >= 4-fold increase at post-vaccination
S-: Pre-vaccination baseline titer is < 1:8; S+: Pre-vaccination baseline titer is >= 1:8
Group 1: MenACYW conjugate vaccine + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Group 2: MENVEO + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Study: MET61 Program: t08204to207.sas Datasets=ADSL ADIS Output: PRODOPS/SP0047/MET61/CSR_01/REPORT/OUTPUT/T08206_i.rtf (08MAR2024 15:31)

hSBA Antibody Titre ≥ 1:4 and ≥ 1:8

In the PPAS3, at pre-dose 2 (6 months after the first vaccination at 6 to 7 months of age), the percentages of subjects with meningococcal hSBA titres ≥ 1:4 and ≥ 1:8 were comparable in both groups for serogroup A and higher in Group 1 than in Group 2 for serogroups C, Y, and W. The percentages of subjects with meningococcal hSBA titres ≥ 1:4 and ≥ 1:8 were:

- for serogroup A: 87.4% and 77.7% in Group 1 and 85.7% and 73.6% in Group 2
- for serogroup C: 99.0% and 98.1% in Group 1 and 77.7% and 69.1% in Group 2
- for serogroup Y: 98.1% and 96.2% in Group 1 and 69.9% and 54.8% in Group 2
- for serogroup W: 98.1% and 96.2% in Group 1 and 61.3% and 50.5% in Group 2

hSBA Meningococcal Serogroups A, C, Y, and W Antibody Titres

Table 20: Summary of geometric means of hSBA titres at pre-dose 2 (6 month after the first vaccination at 6 to 7 months of age) - Per-Protocol Analysis Set 3

	Group 1 (N=108)			Group 2 (N=96)		
Serogroup	M	GMT	(95% CI)	M	GMT	(95% CI)
A	103	20.1	(14.7 ; 27.4)	91	14.9	(11.0 ; 20.3)
C	104	150	(117 ; 193)	94	12.7	(9.63 ; 16.8)
Y	106	46.2	(36.3 ; 58.6)	93	6.74	(5.43 ; 8.36)
W	106	46.8	(36.1 ; 60.5)	93	6.16	(4.87 ; 7.80)

M: number of subjects with available data for the relevant endpoint
N: number of subjects in per-protocol analysis set 3
Group 1: MenACYW conjugate vaccine + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Group 2: MENVEO + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Study: MET61 Program: t08186n187n190n191.sas Datasets=ADSL ADIS Output: PRODOPS/SP0047/MET61/CSR_01/REPORT/OUTPUT/T08190_i.rtf (08MAR2024 15:29)

Antibody Titre ≥ 4-Fold Rise from Pre- to Post-vaccination

In the PPAS2, the percentages of subjects with ≥ 4-fold rise of hSBA titre from pre-dose 2 (6 months after the first vaccination at 6 to 7 months of age) to 30 days after the second vaccination at 12 to 13 months of age were comparable in both groups for all serogroups. The percentages of subjects with a ≥ 4-fold rise of hSBA titre were:

- for serogroup A: 79.7% in Group 1 and 82.9% in Group 2
- for serogroup C: 93.2% in Group 1 and 93.2% in Group 2
- for serogroup Y: 86.5% in Group 1 and 91.8% in Group 2
- for serogroup W: 85.7% in Group 1 and 93.2% in Group 2

Secondary Objective 5: Antibody Responses 30 Days After the Second Vaccination at 20 to 23 Months of Age with MenACYW Conjugate Vaccine or Menactra (Groups 3 and 4)

The secondary objective 5 was to describe the antibody response against meningococcal serogroups A, C, Y, and W 30 days after the second vaccination at 20 to 23 months of age with MenACYW conjugate vaccine (Group 3) or Menactra (Group 4).

hSBA Vaccine Seroresponse

Table 21: Summary of subjects with hSBA vaccine seroresponse from pre-dose 1 to 30 days after the second vaccination at 20 to 23 months of age - Per-Protocol Analysis Set 2

		Group 3 (N=61)			Group 4 (N=65)		
Serogroup	Baseline status	n/M	%	(95% CI)	n/M	%	(95% CI)
A	Any	43/59	72.9	(59.7 ; 83.6)	27/58	46.6	(33.3 ; 60.1)
	S-	33/42	78.6	(63.2 ; 89.7)	25/47	53.2	(38.1 ; 67.9)
	S+	10/17	58.8	(32.9 ; 81.6)	2/11	18.2	(2.3 ; 51.8)
C	Any	59/59	100	(93.9 ; 100)	55/59	93.2	(83.5 ; 98.1)
	S-	58/58	100	(93.8 ; 100)	53/56	94.6	(85.1 ; 98.9)
	S+	1/1	100	(2.5 ; 100)	2/3	66.7	(9.4 ; 99.2)
Y	Any	59/59	100	(93.9 ; 100)	52/59	88.1	(77.1 ; 95.1)
	S-	54/54	100	(93.4 ; 100)	48/54	88.9	(77.4 ; 95.8)
	S+	5/5	100	(47.8 ; 100)	4/5	80.0	(28.4 ; 99.5)
W	Any	59/59	100	(93.9 ; 100)	45/59	76.3	(63.4 ; 86.4)
	S-	59/59	100	(93.9 ; 100)	45/58	77.6	(64.7 ; 87.5)
	S+	0/0	NC	(NC ; NC)	0/1	0	(0 ; 97.5)

n: number of subjects achieving hSBA vaccine seroresponse criteria; M: number of subjects with available data for the relevant endpoint
N: number of subjects in per-protocol analysis set 2
hSBA vaccine seroresponse: titer is < 1:8 at baseline with post-vaccination titer >= 1:16 or titer is >= 1:8 at baseline with a >= 4-fold increase at post-vaccination
S-: Pre-vaccination baseline titer is < 1:8; S+: Pre-vaccination baseline titer is >= 1:8
Group 3: MenACYW conjugate vaccine at 17 to 19 months of age and 20 to 23 months of age
Group 4: Menactra at 17 to 19 months of age and 20 to 23 months of age
Study: MET61 Program: t08216n217.sas Datasets=ADSL ADIS Output: PRODOPS/SP0047/MET61/CSR_01/REPORT/OUTPUT/T08216_i.rtf (08MAR2024 15:31)

hSBA Antibody Titre ≥ 1:4 and ≥ 1:8

Table 22: Number and percentage of subjects with hSBA titre >= 1:4 and >= 1:8 at pre-dose 1 and 30 days after the second vaccination at 20 to 23 months of age - Per-Protocol Analysis Set 2

			Group 3 (N=61)			Group 4 (N=65)		
Serogroup	Time Point	hSBA Titers	n/M	%	(95% CI)	n/M	%	(95% CI)
A	D0 (Pre-Dose 1)	>=1:4	32/59	54.2	(40.8 ; 67.3)	20/59	33.9	(22.1 ; 47.4)
		>=1:8	17/59	28.8	(17.8 ; 42.1)	11/59	18.6	(9.7 ; 30.9)
	D30 (Post-Dose 2)	>=1:4	57/61	93.4	(84.1 ; 98.2)	49/64	76.6	(64.3 ; 86.2)
		>=1:8	54/61	88.5	(77.8 ; 95.3)	40/64	62.5	(49.5 ; 74.3)
C	D0 (Pre-Dose 1)	>=1:4	2/59	3.4	(0.4 ; 11.7)	6/59	10.2	(3.8 ; 20.8)
		>=1:8	1/59	1.7	(0 ; 9.1)	3/59	5.1	(1.1 ; 14.1)
	D30 (Post-Dose 2)	>=1:4	61/61	100	(94.1 ; 100)	64/65	98.5	(91.7 ; 100)
		>=1:8	61/61	100	(94.1 ; 100)	64/65	98.5	(91.7 ; 100)
Y	D0 (Pre-Dose 1)	>=1:4	7/59	11.9	(4.9 ; 22.9)	6/59	10.2	(3.8 ; 20.8)
		>=1:8	5/59	8.5	(2.8 ; 18.7)	5/59	8.5	(2.8 ; 18.7)
	D30 (Post-Dose 2)	>=1:4	61/61	100	(94.1 ; 100)	61/65	93.8	(85.0 ; 98.3)
		>=1:8	61/61	100	(94.1 ; 100)	60/65	92.3	(83.0 ; 97.5)
W	D0 (Pre-Dose 1)	>=1:4	1/59	1.7	(0 ; 9.1)	2/59	3.4	(0.4 ; 11.7)
		>=1:8	0/59	0	(0 ; 6.1)	1/59	1.7	(0 ; 9.1)
	D30 (Post-Dose 2)	>=1:4	61/61	100	(94.1 ; 100)	56/65	86.2	(75.3 ; 93.5)
		>=1:8	61/61	100	(94.1 ; 100)	55/65	84.6	(73.5 ; 92.4)

n: number of subjects experiencing the endpoint; M: number of subjects with available data for the relevant endpoint.
N: number of subjects in per-protocol analysis set 2
Group 3: MenACYW conjugate vaccine at 17 to 19 months of age and 20 to 23 months of age
Group 4: Menactra at 17 to 19 months of age and 20 to 23 months of age
Study: MET61 Program: t08208n209.sas Datasets=ADIS ADSL Output: PRODOPS/SP0047/MET61/CSR_01/REPORT/OUTPUT/T08208_x.pdf (08MAR2024 15:31)

hSBA Meningococcal Serogroups A, C, Y, and W Antibody Titres

Table 23: Summary of geometric means of hSBA titres at pre-dose 1 and 30 days after the second vaccination at 20 to 23 months of age - Per-Protocol Analysis set 2

		Group 3 (N=61)			Group 4 (N=65)		
Serogroup	Time Point	M	GMT	(95% CI)	M	GMT	(95% CI)
A	D0 (Pre-Dose 1)	59	4.29	(3.36 ; 5.49)	59	3.43	(2.61 ; 4.51)
	D30 (Post-Dose 2)	61	45.0	(29.8 ; 68.0)	64	13.2	(8.72 ; 19.9)
C	D0 (Pre-Dose 1)	59	2.10	(1.95 ; 2.26)	59	2.41	(2.01 ; 2.90)
	D30 (Post-Dose 2)	61	1727	(1300 ; 2294)	65	59.4	(44.3 ; 79.6)
Y	D0 (Pre-Dose 1)	59	2.44	(2.07 ; 2.88)	59	2.44	(2.05 ; 2.91)
	D30 (Post-Dose 2)	61	284	(218 ; 369)	65	45.5	(32.9 ; 62.8)
W	D0 (Pre-Dose 1)	59	2.02	(1.98 ; 2.07)	59	2.12	(1.93 ; 2.34)
	D30 (Post-Dose 2)	61	202	(152 ; 267)	65	25.0	(17.6 ; 35.7)

M: number of subjects with available data for the relevant endpoint
N: number of subjects in per-protocol analysis set 2
Group 3: MenACYW conjugate vaccine at 17 to 19 months of age and 20 to 23 months of age
Group 4: Menactra at 17 to 19 months of age and 20 to 23 months of age
Study: MET61 Program: t08188n189n210n211.sas Datasets=ADSL ADIS Output: PRODOPS/SP0047/MET61/CSR_01/REPORT/OUTPUT/T08210_i.rtf (08MAR2024 15:30)

hSBA Antibody Titre ≥ 4-Fold Rise from Pre- to Post-vaccination

In the PPAS2, the percentages of subjects with ≥ 4-fold rise of hSBA titre from pre-dose 1 to 30 days after the second vaccination at 20 to 23 months of age were higher in Group 3 than in Group 4 for serogroup W and numerically higher in Group 3 than in Group 4 for serogroups A, C, and Y. The percentages of subjects with a ≥ 4-fold rise of hSBA titre were:

- for serogroup A: 72.9% in Group 3 and 46.6% in Group 4
- for serogroup C: 100% in Group 3 and 93.2% in Group 4
- for serogroup Y: 100% in Group 3 and 88.1% in Group 4
- for serogroup W: 100% in Group 3 and 76.3% in Group 4

Safety results

Safety Summary After Any Dose- Overall SafAS

Table 24: Safety overview after any vaccine injections - Overall Safety Analysis Set for Any Dose

	Group 1 (N=370)			Group 2 (N=361)			Group 3 (N=96)			Group 4 (N=103)		
Participants experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Within 30 mins after any vaccine injections												
Immediate unsolicited AE	0/370	0	(0 ; 1.0)	1/361	0.3	(0 ; 1.5)	0/96	0	(0 ; 3.8)	0/103	0	(0 ; 3.5)
Immediate unsolicited AR	0/370	0	(0 ; 1.0)	0/361	0	(0 ; 1.0)	0/96	0	(0 ; 3.8)	0/103	0	(0 ; 3.5)
Solicited reaction within solicited period after any vaccine injections	266/356	74.7	(69.9 ; 79.2)	243/342	71.1	(65.9 ; 75.8)	65/91	71.4	(61.0 ; 80.4)	71/100	71.0	(61.1 ; 79.6)
Grade 3 solicited reaction	44/356	12.4	(9.1 ; 16.2)	34/342	9.9	(7.0 ; 13.6)	4/91	4.4	(1.2 ; 10.9)	7/100	7.0	(2.9 ; 13.9)
Solicited injection site reaction	226/356	63.5	(58.2 ; 68.5)	211/342	61.7	(56.3 ; 66.9)	52/91	57.1	(46.3 ; 67.5)	48/100	48.0	(37.9 ; 58.2)
Solicited injection site after injection of MenACYW or MENVEO® or Menactra®	199/356	55.9	(50.6 ; 61.1)	180/342	52.6	(47.2 ; 58.0)	52/91	57.1	(46.3 ; 67.5)	48/100	48.0	(37.9 ; 58.2)
Solicited injection site after injection of Pentacel	93/211	44.1	(37.3 ; 51.1)	79/204	38.7	(32.0 ; 45.8)	-	-	-	-	-	-
Solicited injection site after injection of ENGERIX-B or Recombivax HB	66/184	35.9	(28.9 ; 43.3)	54/178	30.3	(23.7 ; 37.7)	-	-	-	-	-	-
Solicited injection site after injection of Pediarix	71/139	51.1	(42.5 ; 59.6)	71/136	52.2	(43.5 ; 60.8)	-	-	-	-	-	-
Solicited injection site after injection of ActHib or Hiberix or PedvaxHIB	63/124	50.8	(41.7 ; 59.9)	62/126	49.2	(40.2 ; 58.3)	-	-	-	-	-	-
Solicited injection site after injection of Prevnar 13	156/351	44.4	(39.2 ; 49.8)	146/338	43.2	(37.8 ; 48.7)	-	-	-	-	-	-
Solicited injection site after injection of M-M-R II	101/286	35.3	(29.8 ; 41.2)	95/269	35.3	(29.6 ; 41.4)	-	-	-	-	-	-
Solicited injection site after injection of Varivax	101/286	35.3	(29.8 ; 41.2)	96/269	35.7	(30.0 ; 41.7)	-	-	-	-	-	-
Grade 3 injection site reaction	21/356	5.9	(3.7 ; 8.9)	18/342	5.3	(3.1 ; 8.2)	0/91	0	(0 ; 4.0)	1/100	1.0	(0 ; 5.4)
Post-Injection MenACYW or MENVEO® or Menactra®	10/356	2.8	(1.4 ; 5.1)	10/342	2.9	(1.4 ; 5.3)	0/91	0	(0 ; 4.0)	1/100	1.0	(0 ; 5.4)
Solicited systemic reaction	235/356	66.0	(60.8 ; 70.9)	215/342	62.9	(57.5 ; 68.0)	55/91	60.4	(49.6 ; 70.5)	62/100	62.0	(51.7 ; 71.5)
Grade 3 systemic reaction	34/356	9.6	(6.7 ; 13.1)	27/342	7.9	(5.3 ; 11.3)	4/91	4.4	(1.2 ; 10.9)	7/100	7.0	(2.9 ; 13.9)

	Group 1 (N=370)			Group 2 (N=361)			Group 3 (N=96)			Group 4 (N=103)		
Participants experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Within 30 days after any vaccine injections												
Unsolicited AE	182/370	49.2	(44.0 ; 54.4)	154/361	42.7	(37.5 ; 47.9)	36/96	37.5	(27.8 ; 48.0)	37/103	35.9	(26.7 ; 46.0)
Unsolicited AR	11/370	3.0	(1.5 ; 5.3)	9/361	2.5	(1.1 ; 4.7)	3/96	3.1	(0.6 ; 8.9)	4/103	3.9	(1.1 ; 9.6)
Unsolicited non-serious AE	182/370	49.2	(44.0 ; 54.4)	153/361	42.4	(37.2 ; 47.7)	36/96	37.5	(27.8 ; 48.0)	36/103	35.0	(25.8 ; 45.0)
Unsolicited non-serious AR	11/370	3.0	(1.5 ; 5.3)	9/361	2.5	(1.1 ; 4.7)	3/96	3.1	(0.6 ; 8.9)	3/103	2.9	(0.6 ; 8.3)
Unsolicited non-serious injection site AR related to MenACYW or MENVEO® or Menactra®	11/370	3.0	(1.5 ; 5.3)	9/361	2.5	(1.1 ; 4.7)	3/96	3.1	(0.6 ; 8.9)	3/103	2.9	(0.6 ; 8.3)
Unsolicited non-serious injection site AR related to Pentacel	6/370	1.6	(0.6 ; 3.5)	3/361	0.8	(0.2 ; 2.4)	-	-	-	-	-	-
Unsolicited non-serious injection site AR related to ENGERIX-B or Recombivax HB	5/370	1.4	(0.4 ; 3.1)	2/361	0.6	(0.1 ; 2.0)	-	-	-	-	-	-
Unsolicited non-serious injection site AR related to Pediarix	5/370	1.4	(0.4 ; 3.1)	3/361	0.8	(0.2 ; 2.4)	-	-	-	-	-	-
Unsolicited non-serious injection site AR related to ActHib or Hiberix or PedvaxHIB	5/370	1.4	(0.4 ; 3.1)	1/361	0.3	(0 ; 1.5)	-	-	-	-	-	-
Unsolicited non-serious injection site AR related to Prevnar 13	11/370	3.0	(1.5 ; 5.3)	4/361	1.1	(0.3 ; 2.8)	-	-	-	-	-	-
Unsolicited non-serious injection site AR related to M-M-R II	6/370	1.6	(0.6 ; 3.5)	2/361	0.6	(0.1 ; 2.0)	-	-	-	-	-	-
Unsolicited non-serious injection site AR related to Varivax	3/370	0.8	(0.2 ; 2.4)	4/361	1.1	(0.3 ; 2.8)	-	-	-	-	-	-
Unsolicited non-serious systemic AE	176/370	47.6	(42.4 ; 52.8)	150/361	41.6	(36.4 ; 46.8)	35/96	36.5	(26.9 ; 46.9)	34/103	33.0	(24.1 ; 43.0)
Unsolicited non-serious systemic AR	0/370	0	(0 ; 1.0)	0/361	0	(0 ; 1.0)	0/96	0	(0 ; 3.8)	0/103	0	(0 ; 3.5)
AE leading to study discontinuation	0/370	0	(0 ; 1.0)	1/361	0.3	(0 ; 1.5)	0/96	0	(0 ; 3.8)	0/103	0	(0 ; 3.5)
SAE	1/370	0.3	(0 ; 1.5)	2/361	0.6	(0.1 ; 2.0)	0/96	0	(0 ; 3.8)	2/103	1.9	(0.2 ; 6.8)
Death	0/370	0	(0 ; 1.0)	0/361	0	(0 ; 1.0)	0/96	0	(0 ; 3.8)	0/103	0	(0 ; 3.5)
AESI	0/370	0	(0 ; 1.0)	0/361	0	(0 ; 1.0)	0/96	0	(0 ; 3.8)	1/103	1.0	(0 ; 5.3)

Participants experiencing at least one:	Group 1 (N=370) n/M	%	(95% CI)	Group 2 (N=361) n/M	%	(95% CI)	Group 3 (N=96) n/M	%	(95% CI)	Group 4 (N=103) n/M	%	(95% CI)
MAAE	136/370	36.8	(31.8 ; 41.9)	117/361	32.4	(27.6 ; 37.5)	28/96	29.2	(20.3 ; 39.3)	28/103	27.2	(18.9 ; 36.8)
During the study												
SAE	6/370	1.6	(0.6 ; 3.5)	12/361	3.3	(1.7 ; 5.7)	1/96	1.0	(0 ; 5.7)	4/103	3.9	(1.1 ; 9.6)
Death	0/370	0	(0 ; 1.0)	0/361	0	(0 ; 1.0)	0/96	0	(0 ; 3.8)	0/103	0	(0 ; 3.5)
AESI	1/370	0.3	(0 ; 1.5)	2/361	0.6	(0.1 ; 2.0)	0/96	0	(0 ; 3.8)	2/103	1.9	(0.2 ; 6.8)
MAAE	252/370	68.1	(63.1 ; 72.8)	249/361	69.0	(63.9 ; 73.7)	61/96	63.5	(53.1 ; 73.1)	64/103	62.1	(52.0 ; 71.5)

n: number of participants experiencing the endpoint listed in the first column; M: number of participants with available data for the relevant endpoint

N: number of participants 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 event of special interest

AR: Reactions related to investigational medicinal product (IMP) (MenACYW/MENVEO®/Menactra®); Unsolicited injection site reactions related to non-investigational medicinal product (NIMP) (routine vaccines) are reported separately

Group 1: MenACYW conjugate vaccine + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age

Group 2: MENVEO® + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age

Group 3: MenACYW conjugate vaccine at 17 to 19 months of age and 20 to 23 months of age

Group 4: Menactra® at 17 to 19 months of age and 20 to 23 months of age

Table 25: Summary of solicited reactions within 7 days after any vaccine injections - Overall Safety Analysis Set for Any Dose

Subjects experiencing at least one:	Group 1 (N=370) n/M	%	(95% CI)	Group 2 (N=361) n/M	%	(95% CI)	Group 3 (N=96) n/M	%	(95% CI)	Group 4 (N=103) n/M	%	(95% CI)
Solicited reaction	266/356	74.7	(69.9 ; 79.2)	243/342	71.1	(65.9 ; 75.8)	65/91	71.4	(61.0 ; 80.4)	71/100	71.0	(61.1 ; 79.6)
Grade 3 solicited reaction	44/356	12.4	(9.1 ; 16.2)	34/342	9.9	(7.0 ; 13.6)	4/91	4.4	(1.2 ; 10.9)	7/100	7.0	(2.9 ; 13.9)
Solicited injection site reaction	226/356	63.5	(58.2 ; 68.5)	211/342	61.7	(56.3 ; 66.9)	52/91	57.1	(46.3 ; 67.5)	48/100	48.0	(37.9 ; 58.2)
Post-Injection MenACYW or MENVEO or Menactra	199/356	55.9	(50.6 ; 61.1)	180/342	52.6	(47.2 ; 58.0)	52/91	57.1	(46.3 ; 67.5)	48/100	48.0	(37.9 ; 58.2)
Post-Injection Pentacel	93/211	44.1	(37.3 ; 51.1)	79/204	38.7	(32.0 ; 45.8)	-	-	-	-	-	-
Post-Injection ENGERIX-B or Recombivax HB	66/184	35.9	(28.9 ; 43.3)	54/178	30.3	(23.7 ; 37.7)	-	-	-	-	-	-
Post-Injection Pediarix	71/139	51.1	(42.5 ; 59.6)	71/136	52.2	(43.5 ; 60.8)	-	-	-	-	-	-
Post-Injection ActHib or Hiberix or PedvaxHIB	63/124	50.8	(41.7 ; 59.9)	62/126	49.2	(40.2 ; 58.3)	-	-	-	-	-	-
Post-Injection Prevnar 13	156/351	44.4	(39.2 ; 49.8)	146/338	43.2	(37.8 ; 48.7)	-	-	-	-	-	-
Post-Injection M-M-R II	101/286	35.3	(29.8 ; 41.2)	95/269	35.3	(29.6 ; 41.4)	-	-	-	-	-	-
Post-Injection Varivax	101/286	35.3	(29.8 ; 41.2)	96/269	35.7	(30.0 ; 41.7)	-	-	-	-	-	-
Grade 3 injection site reaction	21/356	5.9	(3.7 ; 8.9)	18/342	5.3	(3.1 ; 8.2)	0/91	0	(0 ; 4.0)	1/100	1.0	(0 ; 5.4)
Post-Injection MenACYW or MENVEO or Menactra	10/356	2.8	(1.4 ; 5.1)	10/342	2.9	(1.4 ; 5.3)	0/91	0	(0 ; 4.0)	1/100	1.0	(0 ; 5.4)
Post-Injection Pentacel	10/211	4.7	(2.3 ; 8.5)	5/204	2.5	(0.8 ; 5.6)	-	-	-	-	-	-
Post-Injection ENGERIX-B or Recombivax HB	5/184	2.7	(0.9 ; 6.2)	1/178	0.6	(0 ; 3.1)	-	-	-	-	-	-
Post-Injection Pediarix	2/139	1.4	(0.2 ; 5.1)	4/136	2.9	(0.8 ; 7.4)	-	-	-	-	-	-
Post-Injection ActHib or Hiberix or PedvaxHIB	1/124	0.8	(0 ; 4.4)	4/126	3.2	(0.9 ; 7.9)	-	-	-	-	-	-
Post-Injection Prevnar 13	12/351	3.4	(1.8 ; 5.9)	10/338	3.0	(1.4 ; 5.4)	-	-	-	-	-	-
Post-Injection M-M-R II	5/286	1.7	(0.6 ; 4.0)	6/269	2.2	(0.8 ; 4.8)	-	-	-	-	-	-
Post-Injection Varivax	3/286	1.0	(0.2 ; 3.0)	2/269	0.7	(0.1 ; 2.7)	-	-	-	-	-	-

Subjects experiencing at least one:	Group 1 (N=370) n/M	%	(95% CI)	Group 2 (N=361) n/M	%	(95% CI)	Group 3 (N=96) n/M	%	(95% CI)	Group 4 (N=103) n/M	%	(95% CI)
Solicited systemic reaction	235/356	66.0	(60.8 ; 70.9)	215/342	62.9	(57.5 ; 68.0)	55/91	60.4	(49.6 ; 70.5)	62/100	62.0	(51.7 ; 71.5)
Grade 3 systemic reaction	34/356	9.6	(6.7 ; 13.1)	27/342	7.9	(5.3 ; 11.3)	4/91	4.4	(1.2 ; 10.9)	7/100	7.0	(2.9 ; 13.9)

Safety Overview After the First Vaccination for Group 1 and Group 2 - SAF1

Table 26: Safety overview after vaccine injection 1 at 6 months of age for Group 1 and Group 2 - Safety Analysis Set 1

	Group 1 (N=370)			Group 2 (N=361)		
Participants experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Within 30 mins after any vaccine injections						
Immediate unsolicited AE	0/370	0	(0 ; 1.0)	1/361	0.3	(0 ; 1.5)
Immediate unsolicited AR	0/370	0	(0 ; 1.0)	0/361	0	(0 ; 1.0)
Solicited reaction within solicited period after any vaccine injections	245/351	69.8	(64.7 ; 74.6)	226/339	66.7	(61.4 ; 71.7)
Solicited injection site reaction	197/351	56.1	(50.8 ; 61.4)	184/339	54.3	(48.8 ; 59.7)
Solicited injection site after injection of MenACYW or MENVEO®	166/351	47.3	(42.0 ; 52.7)	144/338	42.6	(37.3 ; 48.1)
Solicited injection site after injection of Pentacel	93/211	44.1	(37.3 ; 51.1)	79/204	38.7	(32.0 ; 45.8)
Solicited injection site after injection of ENGERIX-B or Recombivax HB	66/184	35.9	(28.9 ; 43.3)	54/178	30.3	(23.7 ; 37.7)
Solicited injection site after injection of Pediarix	71/139	51.1	(42.5 ; 59.6)	71/136	52.2	(43.5 ; 60.8)
Solicited injection site after injection of ActHib or Hiberix or PedvaxHIB	63/124	50.8	(41.7 ; 59.9)	62/126	49.2	(40.2 ; 58.3)
Solicited injection site after injection of Prevnar 13	156/351	44.4	(39.2 ; 49.8)	146/338	43.2	(37.8 ; 48.7)
Solicited systemic reaction	209/351	59.5	(54.2 ; 64.7)	193/339	56.9	(51.5 ; 62.3)
Within 30 days after any vaccine injections						
Unsolicited AE	141/370	38.1	(33.1 ; 43.3)	114/361	31.6	(26.8 ; 36.6)
Unsolicited AR	9/370	2.4	(1.1 ; 4.6)	4/361	1.1	(0.3 ; 2.8)
Unsolicited non-serious AE	141/370	38.1	(33.1 ; 43.3)	113/361	31.3	(26.6 ; 36.4)
Unsolicited non-serious AR	9/370	2.4	(1.1 ; 4.6)	4/361	1.1	(0.3 ; 2.8)
Unsolicited non-serious injection site AR related to MenACYW or MENVEO®	9/370	2.4	(1.1 ; 4.6)	4/361	1.1	(0.3 ; 2.8)
Unsolicited non-serious injection site AR related to Pentacel	6/370	1.6	(0.6 ; 3.5)	3/361	0.8	(0.2 ; 2.4)
Unsolicited non-serious injection site AR related to ENGERIX-B or Recombivax HB	5/370	1.4	(0.4 ; 3.1)	2/361	0.6	(0.1 ; 2.0)
Unsolicited non-serious injection site AR related to Pediarix	5/370	1.4	(0.4 ; 3.1)	3/361	0.8	(0.2 ; 2.4)
Unsolicited non-serious injection site AR related to ActHib or Hiberix or PedvaxHIB	5/370	1.4	(0.4 ; 3.1)	1/361	0.3	(0 ; 1.5)
Unsolicited non-serious injection site AR related to Prevnar 13	11/370	3.0	(1.5 ; 5.3)	4/361	1.1	(0.3 ; 2.8)
Unsolicited non-serious systemic AE	132/370	35.7	(30.8 ; 40.8)	108/361	29.9	(25.2 ; 34.9)
Unsolicited non-serious systemic AR	0/370	0	(0 ; 1.0)	0/361	0	(0 ; 1.0)
AE leading to study discontinuation	0/370	0	(0 ; 1.0)	1/361	0.3	(0 ; 1.5)
SAE	0/370	0	(0 ; 1.0)	1/361	0.3	(0 ; 1.5)
Death	0/370	0	(0 ; 1.0)	0/361	0	(0 ; 1.0)
AESI	0/370	0	(0 ; 1.0)	0/361	0	(0 ; 1.0)
MAAE	91/370	24.6	(20.3 ; 29.3)	78/361	21.6	(17.5 ; 26.2)
During the study						
SAE	4/370	1.1	(0.3 ; 2.7)	10/361	2.8	(1.3 ; 5.0)
Death	0/370	0	(0 ; 1.0)	0/361	0	(0 ; 1.0)
AESI	1/370	0.3	(0 ; 1.5)	1/361	0.3	(0 ; 1.5)
MAAE	224/370	60.5	(55.4 ; 65.6)	230/361	63.7	(58.5 ; 68.7)

n: number of participants experiencing the endpoint listed in the first column; M: number of participants with available data for the relevant endpoint
N: number of participants in safety analysis set 1; 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 IMP (MenACYW/MENVEO); Unsolicited injection site reactions related to NIMP (routine vaccines) are reported separately
Group 1: MenACYW conjugate vaccine + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Group 2: MENVEO® + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age

Table 27: Summary of solicited reaction within 7 days after vaccine injection 1 at 6 Months of age for Group 1 and Group 2 - Safety Analysis Set 1

	Group 1 (N=370)			Group 2 (N=361)		
Subjects experiencing at least one:	n/M	%	(95% CI)	n/M	%	(95% CI)
Solicited reaction	245/351	69.8	(64.7 ; 74.6)	226/339	66.7	(61.4 ; 71.7)
Grade 3 solicited reaction	33/351	9.4	(6.6 ; 12.9)	21/339	6.2	(3.9 ; 9.3)
Solicited injection site reaction	197/351	56.1	(50.8 ; 61.4)	184/339	54.3	(48.8 ; 59.7)
Post-Injection MenACYW or MENVEO	166/351	47.3	(42.0 ; 52.7)	144/338	42.6	(37.3 ; 48.1)
Post-Injection Pentacel	93/211	44.1	(37.3 ; 51.1)	79/204	38.7	(32.0 ; 45.8)
Post-Injection ENGERIX-B or Recombivax HB	66/184	35.9	(28.9 ; 43.3)	54/178	30.3	(23.7 ; 37.7)
Post-Injection Pediarix	71/139	51.1	(42.5 ; 59.6)	71/136	52.2	(43.5 ; 60.8)
Post-Injection ActHib or Hiberix or PedvaxHIB	63/124	50.8	(41.7 ; 59.9)	62/126	49.2	(40.2 ; 58.3)
Post-Injection Prevnar 13	156/351	44.4	(39.2 ; 49.8)	146/338	43.2	(37.8 ; 48.7)
Grade 3 injection site reaction	16/351	4.6	(2.6 ; 7.3)	13/339	3.8	(2.1 ; 6.5)
Post-Injection MenACYW or MENVEO	8/351	2.3	(1.0 ; 4.4)	7/338	2.1	(0.8 ; 4.2)
Post-Injection Pentacel	10/211	4.7	(2.3 ; 8.5)	5/204	2.5	(0.8 ; 5.6)
Post-Injection ENGERIX-B or Recombivax HB	5/184	2.7	(0.9 ; 6.2)	1/178	0.6	(0 ; 3.1)
Post-Injection Pediarix	2/139	1.4	(0.2 ; 5.1)	4/136	2.9	(0.8 ; 7.4)
Post-Injection ActHib or Hiberix or PedvaxHIB	1/124	0.8	(0 ; 4.4)	4/126	3.2	(0.9 ; 7.9)
Post-Injection Prevnar 13	12/351	3.4	(1.8 ; 5.9)	10/338	3.0	(1.4 ; 5.4)
Solicited systemic reaction	209/351	59.5	(54.2 ; 64.7)	193/339	56.9	(51.5 ; 62.3)
Grade 3 systemic reaction	25/351	7.1	(4.7 ; 10.3)	17/339	5.0	(2.9 ; 7.9)

N: number of subjects in safety analysis set 1; 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 + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Group 2: MENVEO + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Study: MET61 Program: t08034to38.sas Datasets=ADSL ADRC Output: PRODOPS/SP0047/MET61/CSR_01/REPORT/OUTPUT/T08035_x.pdf (08MAR2024 15:14)

Safety overview after vaccine injection 2 for Group 1 and Group 2 - SAF2

Table 28: Safety overview after vaccine injection 2 at 12 months of age for Group 1 and Group 2 - Safety Analysis Set 2

	Group 1 (N=309)			Group 2 (N=302)		
Participants experiencing at least one:	n/M	%	(95% CI)	n/M	%	(95% CI)
Within 30 mins after any vaccine injections						
Immediate unsolicited AE	0/309	0	(0 ; 1.2)	0/302	0	(0 ; 1.2)
Immediate unsolicited AR	0/309	0	(0 ; 1.2)	0/302	0	(0 ; 1.2)
Solicited reaction within solicited period after any vaccine injections	173/290	59.7	(53.8 ; 65.3)	158/273	57.9	(51.8 ; 63.8)
Solicited injection site reaction	124/289	42.9	(37.1 ; 48.8)	127/272	46.7	(40.6 ; 52.8)
Solicited injection site after injection of MenACYW or MENVEO®	109/289	37.7	(32.1 ; 43.6)	109/272	40.1	(34.2 ; 46.2)
Solicited injection site after injection of M-M-R II	101/287	35.2	(29.7 ; 41.0)	95/267	35.6	(29.8 ; 41.6)
Solicited injection site after injection of Varivax	101/287	35.2	(29.7 ; 41.0)	96/267	36.0	(30.2 ; 42.0)
Solicited systemic reaction	137/290	47.2	(41.4 ; 53.2)	129/273	47.3	(41.2 ; 53.4)
Within 30 days after any vaccine injections						
Unsolicited AE	97/309	31.4	(26.3 ; 36.9)	84/302	27.8	(22.8 ; 33.2)
Unsolicited AR	4/309	1.3	(0.4 ; 3.3)	5/302	1.7	(0.5 ; 3.8)
Unsolicited non-serious AE	97/309	31.4	(26.3 ; 36.9)	84/302	27.8	(22.8 ; 33.2)
Unsolicited non-serious AR	4/309	1.3	(0.4 ; 3.3)	5/302	1.7	(0.5 ; 3.8)
Unsolicited non-serious injection site AR related to MenACYW or MENVEO®	4/309	1.3	(0.4 ; 3.3)	5/302	1.7	(0.5 ; 3.8)
Unsolicited non-serious injection site AR related to M-M-R II	6/309	1.9	(0.7 ; 4.2)	2/302	0.7	(0.1 ; 2.4)
Unsolicited non-serious injection site AR related to Varivax	3/309	1.0	(0.2 ; 2.8)	4/302	1.3	(0.4 ; 3.4)

Participants experiencing at least one:	Group 1 (N=309) n/M	%	(95% CI)	Group 2 (N=302) n/M	%	(95% CI)
Unsolicited non-serious systemic AE	90/309	29.1	(24.1 ; 34.5)	81/302	26.8	(21.9 ; 32.2)
Unsolicited non-serious systemic AR	0/309	0	(0 ; 1.2)	0/302	0	(0 ; 1.2)
AE leading to study discontinuation	0/309	0	(0 ; 1.2)	0/302	0	(0 ; 1.2)
SAE	1/309	0.3	(0 ; 1.8)	1/302	0.3	(0 ; 1.8)
Death	0/309	0	(0 ; 1.2)	0/302	0	(0 ; 1.2)
AESI	0/309	0	(0 ; 1.2)	0/302	0	(0 ; 1.2)
MAAE	67/309	21.7	(17.2 ; 26.7)	60/302	19.9	(15.5 ; 24.8)
During the study						
SAE	2/309	0.6	(0.1 ; 2.3)	3/302	1.0	(0.2 ; 2.9)
Death	0/309	0	(0 ; 1.2)	0/302	0	(0 ; 1.2)
AESI	0/309	0	(0 ; 1.2)	1/302	0.3	(0 ; 1.8)
MAAE	148/309	47.9	(42.2 ; 53.6)	141/302	46.7	(41.0 ; 52.5)

n: number of participants experiencing the endpoint listed in the first column; M: number of participants with available data for the relevant endpoint
N: number of participants in safety analysis set 2; 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 event of special interest.
AR: Reactions related to IMP (MenACYW/MENVEO®); Unsolicited injection site reactions related to NIMP (routine vaccines) are reported separately.
Group 1: MenACYW conjugate vaccine + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Group 2: MENVEO® + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age

Table 29: Summary of solicited reaction within 7 days after vaccine injection 2 at 12 Months of age for Group 1 and Group 2 - Safety Analysis Set 2

Subjects experiencing at least one:	Group 1 (N=309) n/M	%	(95% CI)	Group 2 (N=302) n/M	%	(95% CI)
Solicited reaction	173/290	59.7	(53.8 ; 65.3)	158/273	57.9	(51.8 ; 63.8)
Grade 3 solicited reaction	15/290	5.2	(2.9 ; 8.4)	16/273	5.9	(3.4 ; 9.3)
Solicited injection site reaction	124/289	42.9	(37.1 ; 48.8)	127/272	46.7	(40.6 ; 52.8)
Post-Injection MenACYW or MENVEO	109/289	37.7	(32.1 ; 43.6)	109/272	40.1	(34.2 ; 46.2)
Post-Injection M-M-R II	101/287	35.2	(29.7 ; 41.0)	95/267	35.6	(29.8 ; 41.6)
Post-Injection Varivax	101/287	35.2	(29.7 ; 41.0)	96/267	36.0	(30.2 ; 42.0)
Grade 3 injection site reaction	6/289	2.1	(0.8 ; 4.5)	8/272	2.9	(1.3 ; 5.7)
Post-Injection MenACYW or MENVEO	3/289	1.0	(0.2 ; 3.0)	6/272	2.2	(0.8 ; 4.7)
Post-Injection M-M-R II	5/287	1.7	(0.6 ; 4.0)	6/267	2.2	(0.8 ; 4.8)
Post-Injection Varivax	3/287	1.0	(0.2 ; 3.0)	2/267	0.7	(0.1 ; 2.7)
Solicited systemic reaction	137/290	47.2	(41.4 ; 53.2)	129/273	47.3	(41.2 ; 53.4)
Grade 3 systemic reaction	12/290	4.1	(2.2 ; 7.1)	10/273	3.7	(1.8 ; 6.6)

N: number of subjects in safety analysis set 2; 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 + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Group 2: MENVEO + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Study: MET61 Program: t08034to38.sas Datasets=ADSL ADRC Output: PRODOPS/SP0047/MET61/CSR_01/REPORT/OUTPUT/T08036_x.pdf (08MAR2024 15:14)

Safety overview after the first vaccination for Group 3 and Group 4 - SAF3

Table 30: Safety overview after vaccine injection 1 at 17 months of age for Group 3 and Group 4 - Safety Analysis Set 3

Participants experiencing at least one:	Group 3 (N=96) n/M	%	(95% CI)	Group 4 (N=103) n/M	%	(95% CI)
Within 30 mins after any vaccine injections						
Immediate unsolicited AE	0/96	0	(0 ; 3.8)	0/103	0	(0 ; 3.5)
Immediate unsolicited AR	0/96	0	(0 ; 3.8)	0/103	0	(0 ; 3.5)
Solicited reaction within solicited period after any vaccine injections	56/90	62.2	(51.4 ; 72.2)	62/99	62.6	(52.3 ; 72.1)
Solicited injection site reaction	38/90	42.2	(31.9 ; 53.1)	42/99	42.4	(32.5 ; 52.8)
Solicited systemic reaction	49/90	54.4	(43.6 ; 65.0)	51/99	51.5	(41.3 ; 61.7)
Within 30 days after any vaccine injections						
Unsolicited AE	30/96	31.3	(22.2 ; 41.5)	22/103	21.4	(13.9 ; 30.5)
Unsolicited AR	3/96	3.1	(0.6 ; 8.9)	2/103	1.9	(0.2 ; 6.8)
Unsolicited non-serious AE	30/96	31.3	(22.2 ; 41.5)	22/103	21.4	(13.9 ; 30.5)
Unsolicited non-serious AR	3/96	3.1	(0.6 ; 8.9)	1/103	1.0	(0 ; 5.3)
Unsolicited non-serious injection site AR	3/96	3.1	(0.6 ; 8.9)	1/103	1.0	(0 ; 5.3)
Unsolicited non-serious systemic AE	29/96	30.2	(21.3 ; 40.4)	22/103	21.4	(13.9 ; 30.5)
Unsolicited non-serious systemic AR	0/96	0	(0 ; 3.8)	0/103	0	(0 ; 3.5)
AE leading to study discontinuation	0/96	0	(0 ; 3.8)	0/103	0	(0 ; 3.5)
SAE	0/96	0	(0 ; 3.8)	1/103	1.0	(0 ; 5.3)
Death	0/96	0	(0 ; 3.8)	0/103	0	(0 ; 3.5)
AESI	0/96	0	(0 ; 3.8)	1/103	1.0	(0 ; 5.3)
MAAE	22/96	22.9	(15.0 ; 32.6)	17/103	16.5	(9.9 ; 25.1)
During the study						
SAE	1/96	1.0	(0 ; 5.7)	2/103	1.9	(0.2 ; 6.8)
Death	0/96	0	(0 ; 3.8)	0/103	0	(0 ; 3.5)
AESI	0/96	0	(0 ; 3.8)	2/103	1.9	(0.2 ; 6.8)
MAAE	52/96	54.2	(43.7 ; 64.4)	50/103	48.5	(38.6 ; 58.6)

n: number of participants experiencing the endpoint listed in the first column; M: number of participants with available data for the relevant endpoint
N: number of participants in safety analysis set 3; 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 event of special interest. AR: Reactions related to IMP (MenACYW/Menactra®)
Group 3: MenACYW conjugate vaccine at 17 to 19 months of age and 20 to 23 months of age
Group 4: Menactra® at 17 to 19 months of age and 20 to 23 months of age

Table 31: Summary of solicited reaction within 7 days after vaccine injection 1 at 17 Months of age for Group 3 and Group 4 - Safety Analysis Set 3

Subjects experiencing at least one:	Group 3 (N=96) n/M	%	(95% CI)	Group 4 (N=103) n/M	%	(95% CI)
Solicited reaction	56/90	62.2	(51.4 ; 72.2)	62/99	62.6	(52.3 ; 72.1)
Grade 3 solicited reaction	4/90	4.4	(1.2 ; 11.0)	4/99	4.0	(1.1 ; 10.0)
Solicited injection site reaction	38/90	42.2	(31.9 ; 53.1)	42/99	42.4	(32.5 ; 52.8)
Grade 3 injection site reaction	0/90	0	(0 ; 4.0)	1/99	1.0	(0 ; 5.5)
Solicited systemic reaction	49/90	54.4	(43.6 ; 65.0)	51/99	51.5	(41.3 ; 61.7)
Grade 3 systemic reaction	4/90	4.4	(1.2 ; 11.0)	4/99	4.0	(1.1 ; 10.0)

N: number of subjects in safety analysis set 3; 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 3: MenACYW conjugate vaccine at 17 to 19 months of age and 20 to 23 months of age
Group 4: Menactra at 17 to 19 months of age and 20 to 23 months of age
Study: MET61 Program: t08034to38.sas Datasets=ADSL ADRC Output: PRODOPS/SP0047/MET61/CSR_01/REPORT/OUTPUT/T08037_x.pdf (08MAR2024 15:14)

Safety Overview After Vaccine Injection 2 for Group 3 and Group 4 - SAF4

Table 32: Safety overview after vaccine injection 2 at 20 months of age for Group 3 and Group 4 - Safety Analysis Set 4

	Group 3 (N=86)			Group 4 (N=96)		
Participants experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Within 30 mins after any vaccine injections						
Immediate unsolicited AE	0/86	0	(0 ; 4.2)	0/96	0	(0 ; 3.8)
Immediate unsolicited AR	0/86	0	(0 ; 4.2)	0/96	0	(0 ; 3.8)
Solicited reaction within solicited period after any vaccine injections	53/82	64.6	(53.3 ; 74.9)	52/93	55.9	(45.2 ; 66.2)
Solicited injection site reaction	40/82	48.8	(37.6 ; 60.1)	32/93	34.4	(24.9 ; 45.0)
Solicited systemic reaction	41/82	50.0	(38.7 ; 61.3)	43/93	46.2	(35.8 ; 56.9)
Within 30 days after any vaccine injections						
Unsolicited AE	19/86	22.1	(13.9 ; 32.3)	23/96	24.0	(15.8 ; 33.7)
Unsolicited AR	0/86	0	(0 ; 4.2)	3/96	3.1	(0.6 ; 8.9)
Unsolicited non-serious AE	19/86	22.1	(13.9 ; 32.3)	22/96	22.9	(15.0 ; 32.6)
Unsolicited non-serious AR	0/86	0	(0 ; 4.2)	3/96	3.1	(0.6 ; 8.9)
Unsolicited non-serious injection site AR	0/86	0	(0 ; 4.2)	3/96	3.1	(0.6 ; 8.9)
Unsolicited non-serious systemic AE	19/86	22.1	(13.9 ; 32.3)	19/96	19.8	(12.4 ; 29.2)
Unsolicited non-serious systemic AR	0/86	0	(0 ; 4.2)	0/96	0	(0 ; 3.8)
AE leading to study discontinuation	0/86	0	(0 ; 4.2)	0/96	0	(0 ; 3.8)
SAE	0/86	0	(0 ; 4.2)	1/96	1.0	(0 ; 5.7)
Death	0/86	0	(0 ; 4.2)	0/96	0	(0 ; 3.8)

Table 33: Summary of solicited reaction within 7 days after vaccine injection 2 at 20 Months of age for Group 3 and Group 4 - Safety Analysis Set 4

	Group 3 (N=86)			Group 4 (N=96)		
Subjects experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Solicited reaction	53/82	64.6	(53.3 ; 74.9)	52/93	55.9	(45.2 ; 66.2)
Grade 3 solicited reaction	1/82	1.2	(0 ; 6.6)	4/93	4.3	(1.2 ; 10.6)
Solicited injection site reaction	40/82	48.8	(37.6 ; 60.1)	32/93	34.4	(24.9 ; 45.0)
Grade 3 injection site reaction	0/82	0	(0 ; 4.4)	1/93	1.1	(0 ; 5.8)
Solicited systemic reaction	41/82	50.0	(38.7 ; 61.3)	43/93	46.2	(35.8 ; 56.9)
Grade 3 systemic reaction	1/82	1.2	(0 ; 6.6)	3/93	3.2	(0.7 ; 9.1)

N: number of subjects in safety analysis set 4; 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 3: MenACYW conjugate vaccine at 17 to 19 months of age and 20 to 23 months of age
Group 4: Menactra at 17 to 19 months of age and 20 to 23 months of age
Study: MET61 Program: t08034to38.sas Datasets=ADSL ADRC Output: PRODOPS/SP0047/MET61/CSR_01/REPORT/OUTPUT/T08038_x.pdf (08MAR2024 15:14)

Table 34: Solicited injection site reactions after any vaccine injections, by maximum intensity during the solicited period - Overall Safety

Subjects experiencing at least one:	Maximum intensity	Group 1 (N=370) n/M	%	(95% CI)	Group 2 (N=361) n/M	%	(95% CI)	Group 3 (N=96) n/M	%	(95% CI)	Group 4 (N=103) n/M	%	(95% CI)
MenACYW or MENVEO or Menactra													
Injection site Tenderness	Any	177/356	49.7	(44.4 ; 55.0)	151/341	44.3	(38.9 ; 49.7)	43/91	47.3	(36.7 ; 58.0)	41/100	41.0	(31.3 ; 51.3)
	Grade 1	118/356	33.1	(28.3 ; 38.3)	103/341	30.2	(25.4 ; 35.4)	33/91	36.3	(26.4 ; 47.0)	33/100	33.0	(23.9 ; 43.1)
	Grade 2	50/356	14.0	(10.6 ; 18.1)	40/341	11.7	(8.5 ; 15.6)	10/91	11.0	(5.4 ; 19.3)	7/100	7.0	(2.9 ; 13.9)
	Grade 3	9/356	2.5	(1.2 ; 4.7)	8/341	2.3	(1.0 ; 4.6)	0/91	0	(0 ; 4.0)	1/100	1.0	(0 ; 5.4)
Injection site Erythema	Any	109/355	30.7	(25.9 ; 35.8)	101/342	29.5	(24.7 ; 34.7)	29/91	31.9	(22.5 ; 42.5)	26/100	26.0	(17.7 ; 35.7)
	Grade 1	106/355	29.9	(25.1 ; 34.9)	95/342	27.8	(23.1 ; 32.8)	29/91	31.9	(22.5 ; 42.5)	24/100	24.0	(16.0 ; 33.6)
	Grade 2	3/355	0.8	(0.2 ; 2.4)	4/342	1.2	(0.3 ; 3.0)	0/91	0	(0 ; 4.0)	2/100	2.0	(0.2 ; 7.0)
	Grade 3	0/355	0	(0 ; 1.0)	2/342	0.6	(0.1 ; 2.1)	0/91	0	(0 ; 4.0)	0/100	0	(0 ; 3.6)
Injection site Swelling	Any	80/355	22.5	(18.3 ; 27.2)	71/342	20.8	(16.6 ; 25.5)	23/91	25.3	(16.7 ; 35.5)	14/100	14.0	(7.9 ; 22.4)
	Grade 1	78/355	22.0	(17.8 ; 26.6)	67/342	19.6	(15.5 ; 24.2)	22/91	24.2	(15.8 ; 34.3)	13/100	13.0	(7.1 ; 21.2)
	Grade 2	1/355	0.3	(0 ; 1.6)	3/342	0.9	(0.2 ; 2.5)	1/91	1.1	(0 ; 6.0)	1/100	1.0	(0 ; 5.4)
	Grade 3	1/355	0.3	(0 ; 1.6)	1/342	0.3	(0 ; 1.6)	0/91	0	(0 ; 4.0)	0/100	0	(0 ; 3.6)
Pentacel													
Injection site Tenderness	Any	75/211	35.5	(29.1 ; 42.4)	59/203	29.1	(22.9 ; 35.8)	-	-	-	-	-	-
	Grade 1	51/211	24.2	(18.6 ; 30.5)	38/203	18.7	(13.6 ; 24.8)	-	-	-	-	-	-
	Grade 2	14/211	6.6	(3.7 ; 10.9)	17/203	8.4	(5.0 ; 13.1)	-	-	-	-	-	-
	Grade 3	10/211	4.7	(2.3 ; 8.5)	4/203	2.0	(0.5 ; 5.0)	-	-	-	-	-	-
Injection site Erythema	Any	54/210	25.7	(19.9 ; 32.2)	51/204	25.0	(19.2 ; 31.5)	-	-	-	-	-	-
	Grade 1	48/210	22.9	(17.4 ; 29.1)	50/204	24.5	(18.8 ; 31.0)	-	-	-	-	-	-
	Grade 2	6/210	2.9	(1.1 ; 6.1)	0/204	0	(0 ; 1.8)	-	-	-	-	-	-
	Grade 3	0/210	0	(0 ; 1.7)	1/204	0.5	(0 ; 2.7)	-	-	-	-	-	-
Injection site Swelling	Any	47/210	22.4	(16.9 ; 28.6)	36/204	17.6	(12.7 ; 23.6)	-	-	-	-	-	-
	Grade 1	43/210	20.5	(15.2 ; 26.6)	35/204	17.2	(12.3 ; 23.0)	-	-	-	-	-	-
	Grade 2	4/210	1.9	(0.5 ; 4.8)	0/204	0	(0 ; 1.8)	-	-	-	-	-	-
	Grade 3	0/210	0	(0 ; 1.7)	1/204	0.5	(0 ; 2.7)	-	-	-	-	-	-
ENGERIX-B or Recombivax HB													
Injection site Tenderness	Any	52/184	28.3	(21.9 ; 35.4)	35/177	19.8	(14.2 ; 26.4)	-	-	-	-	-	-
	Grade 1	35/184	19.0	(13.6 ; 25.4)	24/177	13.6	(8.9 ; 19.5)	-	-	-	-	-	-
	Grade 2	12/184	6.5	(3.4 ; 11.1)	10/177	5.6	(2.7 ; 10.1)	-	-	-	-	-	-
	Grade 3	5/184	2.7	(0.9 ; 6.2)	1/177	0.6	(0 ; 3.1)	-	-	-	-	-	-
Injection site Erythema	Any	35/183	19.1	(13.7 ; 25.6)	28/178	15.7	(10.7 ; 21.9)	-	-	-	-	-	-
	Grade 1	34/183	18.6	(13.2 ; 25.0)	28/178	15.7	(10.7 ; 21.9)	-	-	-	-	-	-
	Grade 2	1/183	0.5	(0 ; 3.0)	0/178	0	(0 ; 2.1)	-	-	-	-	-	-
	Grade 3	0/183	0	(0 ; 2.0)	0/178	0	(0 ; 2.1)	-	-	-	-	-	-
Injection site Swelling	Any	23/183	12.6	(8.1 ; 18.3)	17/178	9.6	(5.7 ; 14.9)	-	-	-	-	-	-
	Grade 1	23/183	12.6	(8.1 ; 18.3)	17/178	9.6	(5.7 ; 14.9)	-	-	-	-	-	-
	Grade 2	0/183	0	(0 ; 2.0)	0/178	0	(0 ; 2.1)	-	-	-	-	-	-
	Grade 3	0/183	0	(0 ; 2.0)	0/178	0	(0 ; 2.1)	-	-	-	-	-	-
Pediarix													
Injection site Tenderness	Any	63/139	45.3	(36.9 ; 54.0)	62/136	45.6	(37.0 ; 54.3)	-	-	-	-	-	-
	Grade 1	51/139	36.7	(28.7 ; 45.3)	42/136	30.9	(23.2 ; 39.4)	-	-	-	-	-	-
	Grade 2	10/139	7.2	(3.5 ; 12.8)	16/136	11.8	(6.9 ; 18.4)	-	-	-	-	-	-
	Grade 3	2/139	1.4	(0.2 ; 5.1)	4/136	2.9	(0.8 ; 7.4)	-	-	-	-	-	-

Subjects experiencing at least one:	Maximum intensity	Group 1 (N=370) n/M	%	(95% CI)	Group 2 (N=361) n/M	%	(95% CI)	Group 3 (N=96) n/M	%	(95% CI)	Group 4 (N=103) n/M	%	(95% CI)
Injection site Erythema	Any	38/139	27.3	(20.1 ; 35.5)	34/136	25.0	(18.0 ; 33.1)	-	-	-	-	-	-
	Grade 1	38/139	27.3	(20.1 ; 35.5)	33/136	24.3	(17.3 ; 32.4)	-	-	-	-	-	-
	Grade 2	0/139	0	(0 ; 2.6)	1/136	0.7	(0 ; 4.0)	-	-	-	-	-	-
	Grade 3	0/139	0	(0 ; 2.6)	0/136	0	(0 ; 2.7)	-	-	-	-	-	-
Injection site Swelling	Any	25/139	18.0	(12.0 ; 25.4)	32/136	23.5	(16.7 ; 31.6)	-	-	-	-	-	-
	Grade 1	25/139	18.0	(12.0 ; 25.4)	30/136	22.1	(15.4 ; 30.0)	-	-	-	-	-	-
	Grade 2	0/139	0	(0 ; 2.6)	2/136	1.5	(0.2 ; 5.2)	-	-	-	-	-	-
	Grade 3	0/139	0	(0 ; 2.6)	0/136	0	(0 ; 2.7)	-	-	-	-	-	-
ActHib or Hiberix or PedvaxHIB													
Injection site Tenderness	Any	50/124	40.3	(31.6 ; 49.5)	55/126	43.7	(34.8 ; 52.8)	-	-	-	-	-	-
	Grade 1	39/124	31.5	(23.4 ; 40.4)	38/126	30.2	(22.3 ; 39.0)	-	-	-	-	-	-
	Grade 2	10/124	8.1	(3.9 ; 14.3)	13/126	10.3	(5.6 ; 17.0)	-	-	-	-	-	-
	Grade 3	1/124	0.8	(0 ; 4.4)	4/126	3.2	(0.9 ; 7.9)	-	-	-	-	-	-
Injection site Erythema	Any	30/124	24.2	(17.0 ; 32.7)	31/126	24.6	(17.4 ; 33.1)	-	-	-	-	-	-
	Grade 1	29/124	23.4	(16.3 ; 31.8)	30/126	23.8	(16.7 ; 32.2)	-	-	-	-	-	-
	Grade 2	1/124	0.8	(0 ; 4.4)	1/126	0.8	(0 ; 4.3)	-	-	-	-	-	-
	Grade 3	0/124	0	(0 ; 2.9)	0/126	0	(0 ; 2.9)	-	-	-	-	-	-
Injection site Swelling	Any	18/124	14.5	(8.8 ; 22.0)	23/126	18.3	(11.9 ; 26.1)	-	-	-	-	-	-
	Grade 1	17/124	13.7	(8.2 ; 21.0)	21/126	16.7	(10.6 ; 24.3)	-	-	-	-	-	-
	Grade 2	1/124	0.8	(0 ; 4.4)	2/126	1.6	(0.2 ; 5.6)	-	-	-	-	-	-
	Grade 3	0/124	0	(0 ; 2.9)	0/126	0	(0 ; 2.9)	-	-	-	-	-	-
Prevnar 13													
Injection site Tenderness	Any	135/351	38.5	(33.3 ; 43.8)	114/338	33.7	(28.7 ; 39.0)	-	-	-	-	-	-
	Grade 1	95/351	27.1	(22.5 ; 32.0)	74/338	21.9	(17.6 ; 26.7)	-	-	-	-	-	-
	Grade 2	30/351	8.5	(5.8 ; 12.0)	30/338	8.9	(6.1 ; 12.4)	-	-	-	-	-	-
	Grade 3	10/351	2.8	(1.4 ; 5.2)	10/338	3.0	(1.4 ; 5.4)	-	-	-	-	-	-
Injection site Erythema	Any	86/350	24.6	(20.2 ; 29.4)	86/338	25.4	(20.9 ; 30.4)	-	-	-	-	-	-
	Grade 1	76/350	21.7	(17.5 ; 26.4)	82/338	24.3	(19.8 ; 29.2)	-	-	-	-	-	-
	Grade 2	8/350	2.3	(1.0 ; 4.5)	4/338	1.2	(0.3 ; 3.0)	-	-	-	-	-	-
	Grade 3	2/350	0.6	(0.1 ; 2.0)	0/338	0	(0 ; 1.1)	-	-	-	-	-	-
Injection site Swelling	Any	73/350	20.9	(16.7 ; 25.5)	61/338	18.0	(14.1 ; 22.6)	-	-	-	-	-	-
	Grade 1	64/350	18.3	(14.4 ; 22.7)	57/338	16.9	(13.0 ; 21.3)	-	-	-	-	-	-
	Grade 2	9/350	2.6	(1.2 ; 4.8)	4/338	1.2	(0.3 ; 3.0)	-	-	-	-	-	-
	Grade 3	0/350	0	(0 ; 1.0)	0/338	0	(0 ; 1.1)	-	-	-	-	-	-
M-M-R II													
Injection site Tenderness	Any	85/286	29.7	(24.5 ; 35.4)	81/269	30.1	(24.7 ; 36.0)	-	-	-	-	-	-
	Grade 1	60/286	21.0	(16.4 ; 26.2)	62/269	23.0	(18.2 ; 28.5)	-	-	-	-	-	-
	Grade 2	20/286	7.0	(4.3 ; 10.6)	14/269	5.2	(2.9 ; 8.6)	-	-	-	-	-	-
	Grade 3	5/286	1.7	(0.6 ; 4.0)	5/269	1.9	(0.6 ; 4.3)	-	-	-	-	-	-
Injection site Erythema	Any	49/286	17.1	(13.0 ; 22.0)	50/269	18.6	(14.1 ; 23.8)	-	-	-	-	-	-
	Grade 1	48/286	16.8	(12.6 ; 21.6)	47/269	17.5	(13.1 ; 22.5)	-	-	-	-	-	-
	Grade 2	1/286	0.3	(0 ; 1.9)	2/269	0.7	(0.1 ; 2.7)	-	-	-	-	-	-
	Grade 3	0/286	0	(0 ; 1.3)	1/269	0.4	(0 ; 2.1)	-	-	-	-	-	-
Injection site Swelling	Any	36/286	12.6	(9.0 ; 17.0)	33/269	12.3	(8.6 ; 16.8)	-	-	-	-	-	-
	Grade 1	35/286	12.2	(8.7 ; 16.6)	30/269	11.2	(7.7 ; 15.5)	-	-	-	-	-	-
	Grade 2	1/286	0.3	(0 ; 1.9)	2/269	0.7	(0.1 ; 2.7)	-	-	-	-	-	-
	Grade 3	0/286	0	(0 ; 1.3)	1/269	0.4	(0 ; 2.1)	-	-	-	-	-	-
Varivax													
Injection site Tenderness	Any	85/286	29.7	(24.5 ; 35.4)	81/269	30.1	(24.7 ; 36.0)	-	-	-	-	-	-

Table 35: Solicited systemic reactions after any vaccine injections, by maximum intensity during the solicited period - Overall Safety Analysis

Subjects experiencing at least one:	Maximum intensity	Group 1 (N=370) n/M	%	(95% CI)	Group 2 (N=361) n/M	%	(95% CI)	Group 3 (N=96) n/M	%	(95% CI)	Group 4 (N=103) n/M	%	(95% CI)
Fever	Any	58/347	16.7	(12.9 ; 21.1)	56/330	17.0	(13.1 ; 21.5)	13/90	14.4	(7.9 ; 23.4)	18/100	18.0	(11.0 ; 26.9)
	Grade 1	38/347	11.0	(7.9 ; 14.7)	34/330	10.3	(7.2 ; 14.1)	6/90	6.7	(2.5 ; 13.9)	11/100	11.0	(5.6 ; 18.8)
	Grade 2	17/347	4.9	(2.9 ; 7.7)	18/330	5.5	(3.3 ; 8.5)	6/90	6.7	(2.5 ; 13.9)	6/100	6.0	(2.2 ; 12.6)
	Grade 3	3/347	0.9	(0.2 ; 2.5)	4/330	1.2	(0.3 ; 3.1)	1/90	1.1	(0 ; 6.0)	1/100	1.0	(0 ; 5.4)
Vomiting	Any	42/356	11.8	(8.6 ; 15.6)	37/342	10.8	(7.7 ; 14.6)	7/91	7.7	(3.1 ; 15.2)	9/100	9.0	(4.2 ; 16.4)
	Grade 1	30/356	8.4	(5.8 ; 11.8)	23/342	6.7	(4.3 ; 9.9)	5/91	5.5	(1.8 ; 12.4)	6/100	6.0	(2.2 ; 12.6)
	Grade 2	10/356	2.8	(1.4 ; 5.1)	13/342	3.8	(2.0 ; 6.4)	2/91	2.2	(0.3 ; 7.7)	2/100	2.0	(0.2 ; 7.0)
	Grade 3	2/356	0.6	(0.1 ; 2.0)	1/342	0.3	(0 ; 1.6)	0/91	0	(0 ; 4.0)	1/100	1.0	(0 ; 5.4)
Crying abnormal	Any	160/356	44.9	(39.7 ; 50.3)	138/342	40.4	(35.1 ; 45.8)	35/91	38.5	(28.4 ; 49.2)	34/100	34.0	(24.8 ; 44.2)
	Grade 1	94/356	26.4	(21.9 ; 31.3)	92/342	26.9	(22.3 ; 31.9)	24/91	26.4	(17.7 ; 36.7)	22/100	22.0	(14.3 ; 31.4)
	Grade 2	59/356	16.6	(12.9 ; 20.9)	40/342	11.7	(8.5 ; 15.6)	10/91	11.0	(5.4 ; 19.3)	9/100	9.0	(4.2 ; 16.4)
	Grade 3	7/356	2.0	(0.8 ; 4.0)	6/342	1.8	(0.6 ; 3.8)	1/91	1.1	(0 ; 6.0)	3/100	3.0	(0.6 ; 8.5)
Drowsiness	Any	160/356	44.9	(39.7 ; 50.3)	157/342	45.9	(40.5 ; 51.3)	28/91	30.8	(21.5 ; 41.3)	30/100	30.0	(21.2 ; 40.0)
	Grade 1	114/356	32.0	(27.2 ; 37.1)	107/342	31.3	(26.4 ; 36.5)	21/91	23.1	(14.9 ; 33.1)	23/100	23.0	(15.2 ; 32.5)
	Grade 2	37/356	10.4	(7.4 ; 14.0)	39/342	11.4	(8.2 ; 15.3)	7/91	7.7	(3.1 ; 15.2)	4/100	4.0	(1.1 ; 9.9)
	Grade 3	9/356	2.5	(1.2 ; 4.7)	11/342	3.2	(1.6 ; 5.7)	0/91	0	(0 ; 4.0)	3/100	3.0	(0.6 ; 8.5)
Appetite lost	Any	83/356	23.3	(19.0 ; 28.1)	83/342	24.3	(19.8 ; 29.2)	28/91	30.8	(21.5 ; 41.3)	34/100	34.0	(24.8 ; 44.2)
	Grade 1	56/356	15.7	(12.1 ; 19.9)	67/342	19.6	(15.5 ; 24.2)	21/91	23.1	(14.9 ; 33.1)	23/100	23.0	(15.2 ; 32.5)
	Grade 2	21/356	5.9	(3.7 ; 8.9)	12/342	3.5	(1.8 ; 6.0)	7/91	7.7	(3.1 ; 15.2)	9/100	9.0	(4.2 ; 16.4)
	Grade 3	6/356	1.7	(0.6 ; 3.6)	4/342	1.2	(0.3 ; 3.0)	0/91	0	(0 ; 4.0)	2/100	2.0	(0.2 ; 7.0)
Irritability	Any	202/356	56.7	(51.4 ; 62.0)	186/342	54.4	(48.9 ; 59.8)	44/91	48.4	(37.7 ; 59.1)	52/100	52.0	(41.8 ; 62.1)
	Grade 1	92/356	25.8	(21.4 ; 30.7)	98/342	28.7	(23.9 ; 33.8)	22/91	24.2	(15.8 ; 34.3)	27/100	27.0	(18.6 ; 36.8)
	Grade 2	86/356	24.2	(19.8 ; 28.9)	71/342	20.8	(16.6 ; 25.5)	19/91	20.9	(13.1 ; 30.7)	19/100	19.0	(11.8 ; 28.1)
	Grade 3	24/356	6.7	(4.4 ; 9.9)	17/342	5.0	(2.9 ; 7.8)	3/91	3.3	(0.7 ; 9.3)	6/100	6.0	(2.2 ; 12.6)

N: number of subjects in overall safety analysis set after any dose; n: number of subjects experiencing the endpoint listed in the first 2 columns;
M: number of subjects with available data for the relevant endpoint; Percentages are based on M
Group 1: MenACYW conjugate vaccine + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Group 2: MENVEO + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Group 3: MenACYW conjugate vaccine at 17 to 19 months of age and 20 to 23 months of age
Group 4: Menactra at 17 to 19 months of age and 20 to 23 months of age
Study: MET61 Program: t08079to98.sas Datasets=ADSL ADRC Output: PRODOPS/SP0047/MET61/CSR_01/REPORT/OUTPUT/T08089_i.rtf (08MAR2024 15:23)

Adverse Events of Special Interest

A total of 6 AESIs were reported for 5 subjects during the study. All AESIs were recorded as febrile convulsions according to the MedDRA derived term. The events were reported as febrile seizure for 5 subjects and as febrile convulsions for 1 subject (1 subject in Group 4 experienced 2 AESIs, 1 reported as febrile seizure and the other as febrile convulsions). Febrile seizure was reported for 1 subject in Group 1 (that occurred 119 days after the first vaccination), 2 subjects in Group 2 (1 event occurred 90 days after the first vaccination and the other 97 days after the second vaccination), no subject in Group 3, and 2 subjects in Group 4 (both events occurred 53 days after the first vaccination). None of these AESIs were assessed as related to the study vaccine. One case of Grade 3 febrile convulsions was reported for 1 subject in Group 4 which occurred on Day 1 after the first vaccination with Menactra. This AESI was assessed as related to the study vaccine by the Investigator and the Sponsor.

Other Significant Adverse Events

During the study, there were 252 (68.1%) subjects who reported 1225 MAAEs in Group 1, 249 (69.0%) subjects who reported 1387 MAAEs in Group 2, 61 (63.5%) subjects who reported 238 MAAEs in Group 3, and 64 (62.1%) subjects who reported 258 MAAEs in Group 4. Within 30 days of any vaccination, there were 136 (36.8%) subjects who reported 245 MAAEs in Group 1, 117 (32.4%) subjects who reported 222 MAAEs in Group 2, 28 (29.2%) subjects who reported 67 MAAEs in Group 3, and 28 (27.2%) subjects who reported 53 MAAEs in Group 4.

The main MAAEs (reported during the whole study/including those occurring within 30 days of any vaccination) were:

- Group 1: upper respiratory tract infection (200/38 cases), otitis media (85/16 cases), otitis media acute (65/12 cases), bronchiolitis (49/11 cases), viral infection (41/8 cases), diarrhoea (40/7 cases), pyrexia (35/6 cases), cough (33/5 cases), conjunctivitis (29/6 cases), nasopharyngitis and dermatitis diaper (29/9 cases each), nasal congestion (25/5 cases), candida nappy rash (22/2 cases), viral upper respiratory tract infection (22/3 cases), and constipation (20/6 cases)
- Group 2: upper respiratory tract infection (206/40 cases), otitis media (109/17 cases),otitis media acute (77/13 cases), bronchiolitis (61/9 cases), dermatitis diaper (49/8 cases), diarrhoea (49/7 cases), pyrexia (43/12 cases), viral infection (35/7 cases), viral upper respiratory tract infection (32/3 cases), vomiting (27/3 cases), conjunctivitis (25/6 cases), constipation (24/8 cases), nasal congestion (23/4 cases), bronchitis (23/3 cases), eczema (22/4 cases), nasopharyngitis (21/3 cases) and hand-foot-and-mouth disease (21/0 cases)
- In Group 3: upper respiratory tract infection (33/4 cases), otitis media (17/5 cases), pyrexia (15/6 cases), conjunctivitis (11/1 cases), otitis media acute (9/3 cases), pharyngitis (8/3 cases), bronchiolitis (7/1 cases), bronchitis (7/0 cases), influenza (7/5 cases), cough (7/2 cases), dermatitis diaper (5/1 cases) and ear pain (5/1 cases)
- In Group 4: upper respiratory tract infection (30/4 cases), otitis media (20/5 cases), pyrexia (10/2 cases), otitis media acute (9/2 cases), viral upper respiratory tract infection (7/1 cases), pharyngitis (7/0 cases), gastroenteritis (7/5 cases), eczema (7/0 cases), croup infectious (6/1 cases), dermatitis diaper (6/2 cases), and diarrhoea (6/2 cases), hand-foot-and-mouth disease (5/0 cases), influenza (5/1 cases), impetigo (5/0 cases), and nasal congestion (5/1 cases)

There was 1 MAAE assessed as related to the study vaccine by the Investigator and the Sponsor in Group 1 (1 [0.3%] subject who reported 1 case of injection site reaction that started on the day of vaccination with MenACYW conjugate vaccine). There was no related MAAE reported in Group 2, Group 3, and Group 4. During the study, a total of 11 (3.0%; 15 events) subjects in Group 1, 18 (5.0%; 20 events) in Group 2, 4 (4.2%, 4 events) in Group 3, and 7 (6.8%, 9 events) in Group 4 reported at least 1 Grade 3 MAAE. None was related to study vaccines. A total of 3 (0.8%; 4 events) subjects in Group 1, 5 (1.4%, 5 events) in Group 2, 3 (3.1%, 3 events) in Group 3, and 4 (3.9%, 5 events) reported at least 1 Grade 3 MAAE within 30 days of any vaccination.

2.3.3. Discussion on clinical aspects

Background

MenACYW (MenQuadfi) is authorised in the EU to protect adults and children from the age of 12 months against invasive meningococcal disease caused by four groups of the *Neisseria meningitidis* bacteria (group A, C, W, and Y).

MET61 was a phase III, modified double-blind, randomized parallel group, active-controlled, multi centre immunogenicity and safety study to compare the immunogenicity and describe the safety of MenACYW and Menveo when administered in a 1 + 1 schedule administered concomitantly with routine paediatric vaccines in healthy infants and toddlers in the US. Additionally, this study described safety and immunogenicity of MenACYW compared to Menactra, when administered in a 1 + 1 schedule to healthy toddlers in the US. The study report of MET61 was submitted within 6 months of study completion as required under Article 46 of Regulation (EC) No. 1901/2006, as amended. This study is part of a data package of 5 clinical studies covering individuals 6 to 12 months of age (MET33, MET41,

MET42, MET52, MET58, MET61). The Applicant intends to submit this package in Q1 2025 in a type II variation. Currently, no SmPC changes are foreseen. This approach is acceptable.

Key issues identified are described below and are expected to be addressed by the MAH as part of the type II variation.

Study design & conduct

In MET61, healthy infants received either MenACYW (Group 1) or Menveo (Group 2) concomitantly with routine paediatric vaccines at 6 to 7, and 12 to 13 months of age, and healthy toddlers received either MenACYW (Group 3) or Menactra (Group 4) at 17 to 19, and 20 to 23 months of age. Concomitant vaccines were diphtheria, tetanus and acellular pertussis (DTaP), inactivated poliovirus (IPV), Haemophilus influenzae type b (if not immunized with PedvaxHIV at 2 and 4 months of age), Rotavirus (RotaTeq), and Hepatitis B at 6 months of age; at 6 and 13 months, participants received pneumococcal 13-valent conjugate vaccine (Prevnar 13); and at 12 months of age, participants received measles, mumps, and rubella (M-M-R II), and Varicella (Varivax).

In- and exclusion criteria (related to age, vaccination history, immunodeficiency, etc.) adequately define the study population of interest.

Efficacy and safety of Menveo have not been established in children <2 years of age, and Menactra is not authorized in the EU. Therefore, the use of Menveo and Menactra as comparators should be discussed at the planned type II variation. MET61 did not include non-concomitant comparator groups (e.g. receiving only MenACYW or only other paediatric vaccines), which needs to be taken into account for all results (immunogenicity and safety). At the time of the type II variation it is expected that the MAH will provide data from their paediatric development program to demonstrate that concomitant vs. separate MenACYW vaccination does not negatively impact on immunogenicity (of MenACYW and concomitant vaccines) and safety. Furthermore, the MAH should justify and contextualize the used concomitant vaccines and schedule with the European situation (i.e. available vaccines and recommended vaccination schedules).

A total of 950 participants were randomised in the study: 380 to Group 1, 370 to Group 2, 96 to Group 3 and 104 to Group 4. A slightly larger proportion of subjects in groups 1 and 2 were male than female, although the proportions were balanced between the compared groups and therefore, this is not considered problematic. Baseline demographics were generally well balanced between Group 1 and 2, and between 3 and 4 with regards to age, racial origin, and ethnicity.

A total of 765 (80.5%) participants completed the study: 298 (78.4%) subjects in Group 1, 290 (78.4%) subjects in Group 2, 83 (86.5%) subjects in Group 3, and 94 (90.4%) subjects in Group 4. The proportions of patients who received study drug, concomitant vaccines, and finished the study were similar between groups 1 and 2. Overall, the proportions of patients exposed to the respective vaccines at the respective time points are considered comparable and discontinuation rates/ failure to provide blood samples are not unexpected given the paediatric population.

Blood samples for immunogenicity were drawn in all participants at baseline, and 30 days after the second vaccination. Additionally, in Group 1 and 2, 50% of patients provided blood samples 30 days after the first dose of study drug and the remaining 50% provided a blood sample before the second vaccination. This is considered appropriate to characterise the (short-term) humoral immune response.

The assessment of comparability of MenACYW, Menveo and Menactra is hampered by the lack of discussion of the impact of major protocol deviations and the indirect impact of the COVID-19 pandemic. While the proportion of subjects with at least one major protocol deviation was similar between respective treatment groups (67.9%, 69.2%, 43.8%, 42.3% of subjects in Group 1, 2, 3, and 4 respectively), this is considered to be very high overall. Originally, the sample size was planned to

result in 522 evaluable subjects in the PP set for Group 1 and Group 2, which turned out to be only 343. The largest part of these major protocol deviations consisted of missed samples, samples outside the protocol-specified time window and failure to receive IMP or co-administered vaccine. A total of 35 subjects in Group 1, 36 subjects in Group 2, 6 subjects in Group 3, and 5 subjects in Group 4 were impacted directly by COVID-19, with the non-direct impact of COVID-19 on immunogenicity and safety in general not being discussed by the applicant. The lack of discussion of the impact of the large number of major protocol deviations leading to exclusion from the PP set is considered to be concerning. It is unclear how much the larger than anticipated number of non-evaluable subjects could have affected the study integrity and to what degree corresponding results address a relevant target of estimation. At the time of the intended type II variation, the Applicant is asked to clarify the estimand intended by the study, together with definitions of intercurrent events, their handling in the statistical analysis and conduct sensitivity analysis to evaluate the robustness of the study results with respect to deviations from assumptions made in the statistical analysis.

Immunogenicity

The primary objective was to demonstrate non-inferiority of the vaccine seroresponse to meningococcal serogroups A,C, Y, W following the sequential administration of 2 doses of MenACYW (Group1) compared to Menveo (Group 2) as measured with hSBA. Seroresponse success was dependent on pre-vaccination titres: for a participant with a pre-vaccination titre < 1:8, the post-vaccination titre should be ≥ 1:16 and for a participant with a pre-vaccination titre ≥ 1:8, the post-vaccination titre should be ≥ 4-fold greater than the pre-vaccination titre. This is acceptable, as titre baseline values are considered and do not distort findings. Non-inferiority was to be determined, if the lower limit of the 95% CI of the difference in the proportion of participants with an hSBA seroresponse rate for meningococcal serogroups A, C, W, and Y was greater than -10%. This condition was met for the PPAS2 and the FAS2, which supports non-inferiority of MenACYW compared to Menveo. GMTs at baseline against all 4 serogroups were comparable between all 4 study groups. For individuals 6-7 months of age at baseline, 30 days post-dose 2, GMTs were 1.5-4.6 times higher for MenACYW vaccinated individuals (Group 1) compared to those receiving Menveo (Group 2), with the proportion of subjects with a positive seroresponse being higher for serogroups A and W for MenACYW than Menveo (89.4% vs. 82.9% and 99.3% vs. 92.9%) in the PPAS2. Similarly, for individuals 12-13 months of age at baseline, 30 days post-dose 2, GMTs against all 4 serogroups were 3.4-29.1 times higher in MenACYW vaccinated individuals (Group 3) compared to Menactra (Group 4).

The secondary immunogenicity objectives (including e.g. NI of the percentage of subjects with hSBA titres ≥1:8 and antibody response against meningococcal serogroups 30 days after first, and second vaccination in both age groups) evaluated in trial MET61 are overall considered to be supportive of the primary objective. Overall, it can be concluded from MET61 that humoral immune responses induced by MenACYW are non-inferior as induced by Menveo in the setting of concomitant vaccination with other childhood vaccines.

Importantly, however, immunogenicity was only evaluated for meningococcal vaccines (MenACYW, Menveo, and Menactra), but not for concomitant vaccines. Therefore, from study MET61 it is unclear if MenACYW interferes with immune responses generated by concomitant vaccines. At the time of the intended paediatric type II variation, the Applicant needs to demonstrate that concomitant vaccination with MenACYW and routinely used childhood vaccines does not negatively impact on immunogenicity of the latter.

Safety

Safety data were presented descriptively for the overall safety set SafAS. The SafAS included a total of 930 individuals, 370 subjects in Group, 361 subjects in Group 2 and 96 subjects in Group 3 and 103

subjects in Group 4. Additionally, subjects receiving dose 1 and 2 in the two age groups were included in separate safety sets. SafAS1 included subjects receiving dose 1 at 6 to 7 months and SafAS2 included subjects receiving dose 2 at 12 to 13 months of age (Group 1 and 2), while SafAS3 included subjects receiving dose 1 at 17 to 19 months and SafAS4 included subjects receiving dose 2 at 20 to 23 months of age (Group 3 and 4).

Immediate unsolicited systemic adverse events (AEs) were collected within 30 minutes after each vaccination. Solicited AE information for both solicited injection site reactions and solicited systemic reactions was collected from D0 up to D07 after each vaccination; unsolicited AE information was collected from D0 up to D30 after each vaccination; serious adverse event (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. This is considered appropriate. In the SafAS 71.1-74.7% of subjects experienced a solicited reaction after any vaccine injection across Groups 1-4. The proportion of subjects with Grade 3 solicited reactions was comparable between Group 1 and 2 (12.4% vs. 9.9%) and between Group 3 and 4 (4.4% vs. 7.0%). Overall, injection site reactions such as swelling or erythema were similar between Groups 1 and 2 (63.5% vs. 61.7%), and higher for Group 3 compared to Group 4 (57.1% vs. 48.0%). At the site of injection of the concomitant vaccines, a comparable number of injection site reactions were observed overall (63.5%, 61.7%), although the incidence was numerically higher in Group 1 than Group 2 for Pentacel (44.1% vs. 38.7%) and ENGERIX-B or Recombinax HB (35.9% vs. 30.3%). Injection site reactions of Grade 3 were observed for a similar proportion of subjects for Group 1 and 2 (5.9% vs. 5.3%), while between Groups 3 and 4 only 1 event occurred in Group 4 (1%) compared to none in Group 3.

At least one unsolicited AE within 30 days of vaccination was reported in a numerically higher proportion of subjects in Group 1 compared to Group 2 (49.2% vs. 42.7%) while for Groups 3 and 4 it was similar (37.5% vs. 35.9%). The proportion of subjects with unsolicited non-serious systemic AEs was higher in Group 1 compared to Group 2 (47.6% and 41.6%) and slightly higher for Group 3 compared to Group 4 (36.5% vs 33.0%). The proportion of subjects with at least one non-serious AR was similar between all 4 treatment groups (3%, 2.5%, 3.1%, 3.9% for Groups 1, 2, 3, and 4, respectively).

The proportion of subjects who experienced at least one SAE was overall comparable between the treatment groups (1.6%, 3.3%, 1.0%, and 3.9% for Groups 1, 2, 3, and 4, respectively). None of the SAEs observed in the study (including e.g. acute myeloid leukaemia, bronchiolitis, febrile seizure) was considered related to MenACYW. A total of 6 AESIs were reported for 5 subjects during the study, all of which were recorded as febrile convulsions. There was 1 (0.3%) subject in Group 1, 2 (0.6%) and subjects in Group 2, who experienced one AESI each and 2 (1.9%) subjects in Group 4 who experienced 3 AESIs. In Group 4, one subject had febrile convulsion on day 1 after the first dose of Menactra, which was considered related to IP. All seizures that were considered unrelated occurred at least 50 days after injection. Therefore, no timely relationship with MenACYW vaccination becomes immediately apparent. The proportion of subjects who experienced at least 1 MAAE was similar between the respective groups (36.8%, 32.4%, 29.2%, and 27.2% in Groups 1, 2, 3, and 4, respectively). Only one subject in the Menveo group reported an AE leading to study continuation (acute myeloid leukaemia) 5 days after the first visit, which was considered as unrelated to study vaccine, and no deaths were reported during the study. No deaths occurred.

Overall, no safety findings that would be considered of concern became apparent in the setting of concomitant administration of routinely used paediatric vaccines and MenACYW vs. Menveo or Menactra.

3. CHMP overall conclusion and recommendation

The presented immunogenicity results from study MET61 are generally considered to be supportive of non-inferiority of MenACYW compared to Menveo in the setting of concomitant administration with routinely used paediatric vaccines. No concerning safety findings became apparent.

However, the following issues were identified that will need to be addressed as part of the paediatric development program for the planned type II variation:

1. The lack of discussion of the impact of the large number of major protocol deviations leading to exclusion from the PP set is considered to be concerning. It is unclear how much the larger than anticipated number of non-evaluable subjects could have affected the study integrity and to what degree corresponding results address a relevant target of estimation. The Applicant is asked to clarify the estimand intended by the study, together with definitions of intercurrent events, their handling in the statistical analysis and conduct sensitivity analysis to evaluate the robustness of the study results with respect to deviations from assumptions made in the statistical analysis.
2. Efficacy and safety of Menveo have not been established in children <2 years of age, and Menactra is not authorised in the EU. Therefore, the use of Menveo and Menactra as comparators and applicability of this comparison to EU should be discussed.
3. No non-concomitant vaccination group was included in MET61, thus no comparisons of administration of MenACYW vs. MenACYW + routine childhood vaccines can be made. Further data and/or justifications are required. Furthermore, the MAH should justify and contextualize the used concomitant vaccines and schedule with the European situation (i.e. available vaccines and recommended vaccination schedules).
4. The influence of MenACYW on humoral immune responses of concomitantly administered routine childhood vaccines was not investigated. It needs to de demonstrated that immune responses of the latter are not compromised in the concomitant setting.

☒ Fulfilled:

No regulatory action required.

4. Request for supplementary information

None.

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

The studies should be listed by chronological date of completion:

Non clinical studies

Not applicable.

Clinical studies

Product Name: MenQuadfi

Active substance:

Neisseria meningitidis group A polysaccharide

Neisseria meningitidis group C polysaccharide

Neisseria meningitidis group Y polysaccharide

Neisseria meningitidis group W polysaccharide

Conjugated to tetanus toxoid carrier protein

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