25 January 2024
EMA/59046/2024
Human Medicines Division

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

MenQuadfi

Meningococcal Group A, C, W and Y conjugate vaccine

Procedure no: EMEA/H/C/005084/P46/009

Note

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

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Table of contents

List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
BL	blood sampling
CCDS	Company Core Data Sheet
CEO	critical expert overview
CSR	clinical study report
DTaP-IPV-HB-Hib	diphtheria, tetanus, acellular pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FAS	full analysis set
GMT	geometric mean titer
hSBA	serum bactericidal antibody assay using human complement
MAH	marketing authorization holder
MMR	measles-mumps-rubella
NIC	National Immunization Calendar (The Russian Federation)
PCV13	pneumococcal 13-valnt conjugate vaccine
PIP	Pediatric Investigational Plan
PPAS	per-protocol analysis set
PSUR	Periodic Safety Update Report
rSBA	serum bactericidal antibody assay using baby rabbit complement
SAE	serious adverse event
SafAS	safety analysis set
SD	standard deviation
SmPC	Summary of Product Characteristics

1. Introduction

On 23-Oct-2023, the MAH submitted a completed paediatric study MET33 for MenQuadfi in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study MET33 “Safety and Immunogenicity of a 3-Dose Schedule of an Investigational Quadrivalent Meningococcal Conjugate Vaccine when Administered Concomitantly with Routine Paediatric Vaccines in Healthy Infants and Toddlers” is part of a clinical development program to support a future age indication extension (6 weeks and older) in the EU. The intended type II variation application consisting of the full relevant data package (i.e., ongoing paediatric clinical studies covering 6 weeks to 12 months population: MET33, MET41, MET42, MET52, MET58, MET61) is expected to be submitted by Q1/2025. A line listing of all the concerned studies is annexed.

Study MET33 is included in the MenQuadfi Paediatric Investigational Plan, EMEA-001930-PIP01-16-M04.

2.2. Information on the pharmaceutical formulation used in the study

The formulation of MenQuadfi (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 one study:

- Study MET33: Safety and Immunogenicity of a 3-Dose Schedule of an Investigational Quadrivalent Meningococcal Conjugate Vaccine when Administered Concomitantly with Routine Paediatric Vaccines in Healthy Infants and Toddlers

2.3.2. Clinical study MET33

Description

MET33 is a phase III, open-label, randomised, parallel-group, active-controlled, multi-centre study to describe the immunogenicity and safety of a 3-dose immunisation schedule of MenACYW conjugate vaccine or a 4-dose immunisation schedule of a licensed quadrivalent meningococcal conjugate vaccine (*Menveo*) when administered concomitantly with routine paediatric vaccines (*Prevnar 13, Hexacima, RotaTeq, and M-M-RII*) in healthy infants and toddlers aged 2 to 12 months in Mexico, and to describe the immunogenicity and safety of a 3-dose immunisation schedule of MenACYW conjugate vaccine when administered concomitantly with routine paediatric vaccines (*Prevnar 13®, Pentaxim®,*

ENGERIX-B®, and *MMR*) in healthy infants and toddlers aged 2 to 12 months in the Russian Federation.

MET33 was conducted at 11 centres that enrolled participants in The Russian Federation (8 centres) and The United Mexican States (Mexico) (3 centres).

MET33 that was conducted between 17 October 2018 (first subject first visit) and 18 February 2022 (last subject last visit).

Methods

Study participants

A total of 525 subjects were planned to be enrolled. Approximately 300 healthy, meningococcal vaccine naïve infants aged 2 months were randomised in a 2:1 ratio in Mexico, and 225 healthy, meningococcal-vaccine naïve infants aged 2 months were randomised in a 2:1 ratio in the Russian Federation.

Informed consent form has been signed and dated by the parent(s) or guardian(s), as required by local regulations.

The study population included healthy infants born after a full-term pregnancy, 60 to 89 days of age on the day of the first study visit.

Subjects were excluded from study enrolment if they participated in another clinical trial up to 4 weeks preceding the first trial vaccination; if they received any vaccine in the 4 weeks preceding the first trial vaccination (except for influenza vaccination, which may be received at a gap of at least 2 weeks before or 2 weeks after any study vaccination); if previously vaccinated against meningococcal disease, diphtheria, tetanus, pertussis, Haemophilus influenzae type b, poliovirus, rotavirus, Streptococcus pneumoniae, measles, mumps, rubella, and / or varicella (for Mexico: More than 1 previous dose of hepatitis B vaccine); if they had a history of infection with Neisseria meningitidis or diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, hepatitis A, measles, mumps, rubella, Haemophilus influenzae type b, Streptococcus pneumoniae, and /or rotavirus infection/disease; if they received immune globulins, blood or blood-derived products since birth; if they have known or suspected congenital or acquired immunodeficiency or received immunosuppressive therapy; if they had blood dyscrasias, leukaemia, lymphoma of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems or active tuberculosis; if they had a history of any neurologic disorder (seizures, progressive neurologic disorders, Guillain-Barré syndrome); if they had a 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; if the subject reported thrombocytopenia contraindicating IM vaccination in the Investigator's; if they had a bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating IM vaccination in the Investigator's opinion; if they received oral or injectable antibiotic therapy within 72 hours of the first blood draw.

Treatments

Table 1: Schedule of vaccinations and blood draws in Mexico (Group 1 and Group 2) - Study MET33

Visit (V)	V01	V02	V03	V04	V05	V06*
Subject Age	**2 months**	**4 months**	**6 months**	**7 months**	**12 months***	**13 months**
Group 1	**MenACYW†** Prevnar 13® Hexacima® RotaTeq® **BL0001** (Pre-Vaccination)	Prevnar 13® Hexacima® RotaTeq®	**MenACYW†** Prevnar 13® Hexacima® RotaTeq®	**BL0002**	**MenACYW†** Prevnar 13® Hexacima® M-M-R®II	**BL0003**
Group 2	**Menveo®** Prevnar 13® Hexacima® RotaTeq® **BL0001** (Pre-Vaccination)	**Menveo®** Prevnar 13® Hexacima® RotaTeq®	**Menveo®** Prevnar 13® Hexacima® RotaTeq®	**BL0002**	**Menveo®** Prevnar 13® Hexacima® M-M-R®II	**BL0003**

*Per the current National Immunization Program (NIP) and Health Authority recommendations in Mexico, the varicella vaccine was administered at or after 12 months of age; it was not administered within the scope of the study. However, VARIVAX® vaccine was provided by the Sponsor as a benefit vaccine as per standard practices and the current recommendations of the NIP in Mexico. The study personnel / Investigator was responsible for administering this vaccine at V6 after the last blood sample (BL0003) of the study. No endpoints were measured for this vaccine, even if it was administered at V6 of the study.

†MenACYW conjugate vaccine

Table 2: Schedule of vaccinations and blood draws in the Russian Federation (Group 3 and Group 4) - Study MET33

Visit (V)	V0	V01	V02	V03	V04	V05	V06	V07
Subject Age	**2 months**	**2 months**	**3 months**	**4.5 months**	**6 months**	**7 months**	**12 months**	**13 months**
Group 3	**BL0001** (6 mL) **UA** (8 mL)	Prevnar 13®†	**MenACYW*** Pentaxim®‡	Prevnar 13®† Pentaxim®‡	**MenACYW*** Pentaxim®‡ ENGERIX-B®	**BL0002** (6 mL)	**MenACYW*** MMR	**BL0003** (6 mL) **UA** (8 mL)
Group 4	**BL0001** (6 mL) **UA** (8 mL)	Prevnar 13®†	Pentaxim®‡	Prevnar 13®† Pentaxim®‡	Pentaxim®‡ ENGERIX-B®	**BL0002** (6 mL)	MMR	**BL0003** (6 mL) **UA** (8 mL)

V: Visit, UA: Urinalysis

*MenACYW conjugate vaccine

† No immunogenicity endpoints were measured for this vaccine in the Russian Federation. The PCV13 routine vaccine recommended at 15 months of age in the Russian Federation was considered as out of scope for this study and was provided by the Sponsor but procured by the sites as per their standard practices.

‡The 4th dose of Pentaxim®, which was administered at 18 months of age, was considered out of the scope of the study, and it was not provided by the Sponsor but procured by the sites as per their standard practices. Subjects were instructed to receive it for completion of the Pentavalent series as per the NIC of the Russian Federation recommendation.

Objective(s)

Primary Objectives

1) To describe the vaccine seroprotection (antibody titer ≥1:8) to the antigens (meningococcal serogroups A, C, Y, and W) present in MenACYW conjugate vaccine or Menveo® measured by hSBA, for Groups 1 and 2, when administered concomitantly with routine paediatric vaccines in healthy infants and toddlers in Mexico;

2) To describe the vaccine seroprotection (antibody titer ≥1:8) to the antigens (meningococcal serogroups A, C, Y, and W) present in MenACYW conjugate vaccine measured by hSBA, for Group 3, when administered concomitantly with routine paediatric vaccines in healthy infants and toddlers in the Russian Federation.

Secondary Objectives

1) To describe the hSBA vaccine seroresponse to the antigens (meningococcal serogroups A, C, Y, and W) for Groups 1 and 2, 30 days after the last vaccination of the infant series (Dose 2 of MenACYW conjugate vaccine and Dose 3 of Menveo®), when administered concomitantly with routine paediatric vaccines in healthy infants and toddlers in Mexico;

2) To describe the hSBA vaccine seroresponse to the antigens (meningococcal serogroups A, C, Y, and W) for Group 3, 30 days after the last vaccination of the infant series (Dose 2 of MenACYW conjugate vaccine), when administered concomitantly with routine paediatric vaccines in healthy infants and toddlers in the Russian Federation;

3) To describe the immunogenicity profile of routine paediatric vaccines when administered concomitantly with MenACYW conjugate vaccine (Groups 1 and 3), Menveo® (Group 2), or when administered alone (Group 4);

4) To describe the hSBA antibody responses against meningococcal serogroups A, C, Y, and W when MenACYW conjugate vaccine and Menveo® are administered concomitantly with routine paediatric vaccines in Mexico and the Russian Federation (Groups 1, 2, and 3);

5) To describe the antibody titers to the antigens (meningococcal serogroups A, C, Y, and W) present in MenACYW conjugate vaccine and Menveo® measured by serum bactericidal assay using baby rabbit complement (rSBA) before the first vaccination (Visit 1) and 30 days after the last vaccination of the infant series (Dose 2 of MenACYW conjugate vaccine and Dose 3 of Menveo®), when administered concomitantly with routine paediatric vaccines in a subset of subjects (100 subjects per group in Groups 1 and 50 subjects in Group 2) in Mexico;

6) To describe the antibody titers to the antigens (meningococcal serogroups A, C, Y, and W) present in MenACYW conjugate vaccine measured by rSBA before the first vaccination (Visit 1) and 30 days after the last vaccination of the infant series (Dose 2 of MenACYW conjugate vaccine), when administered concomitantly with routine paediatric vaccines in a subset of subjects (100 subjects in Group 3) in the Russian Federation;

7) To describe the antibody titers to the antigens (meningococcal serogroups A, C, Y, and W) present in MenACYW conjugate vaccine and Menveo® measured by rSBA before the first vaccination (Visit 1) and 30 days after the last vaccination in the second year of life, when administered concomitantly with routine paediatric vaccines in a subset of subjects (100 subjects in Group 1 and 50 subjects in Group 2) in Mexico;

8) To describe the antibody titers to the antigens (meningococcal serogroups A, C, Y, and W) present in MenACYW conjugate vaccine measured by rSBA before the first vaccination (Visit 1 and 30 days after the last vaccination in the second year of life, when administered concomitantly with routine paediatric vaccines in a subset of subjects (100 subjects in Group 3) in the Russian Federation.

Observational Objectives

1) To describe the safety profile of MenACYW conjugate vaccine and Menveo® when administered concomitantly with routine paediatric vaccines in healthy infants and toddlers in Mexico (Group 1 vs Group 2);

2) To describe the safety profile of MenACYW conjugate vaccine when administered concomitantly with routine paediatric vaccines in healthy infants and toddlers in the Russian Federation (Group 3);

3) To describe the safety profile of routine paediatric vaccines in healthy infants and toddlers in Mexico (Groups 1 and 2) and the Russian Federation (Groups 3 and 4).

Outcomes/endpoints

Primary Endpoints

1) Meningococcal serogroups A, C, Y, and W antibody titers ≥ 1:8 measured by hSBA, assessed at 30 days after the last vaccination in the second year of life with MenACYW conjugate vaccine or Menveo® in Mexico (Group 1 and Group 2);

2) Meningococcal serogroups A, C, Y, and W antibody titers ≥ 1:8 measured by hSBA assessed at 30 days after the last vaccination in the second year of life with MenACYW conjugate vaccine in the Russian Federation (Group 3).

Secondary Endpoints

1) Meningococcal serogroups A, C, Y, and W antibody titers measured by hSBA, before the first vaccination (Visit 1) and 30 days after the last vaccination of the infant series with MenACYW conjugate vaccine or Menveo® (Dose 2 of MenACYW conjugate vaccine and Dose 3 of Menveo® in Mexico (Group 1 and Group 2) (vaccine seroresponse);

2) Meningococcal serogroups A, C, Y, and W antibody titers measured by hSBA, before the first vaccination (Visit 1) and 30 days after the last vaccination of the infant series with MenACYW conjugate vaccine (Dose 2 of MenACYW conjugate vaccine) in the Russian Federation (Group 3) (vaccine seroresponse);

3) The following serological endpoints will be described for Mexico (Groups 1 and 2):

- Day 0 (before the first vaccinations with Hexacima® and RotaTeq®):
  - Anti-pertussis antibody concentrations (PT and FHA)
  - Anti-rotavirus serum immunoglobulin (Ig) A antibody concentrations
- 30 days after the 6-months vaccinations with Prevnar 13® and RotaTeq®:
  - Anti-pneumococcal antibody concentrations for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F
  - Anti-pneumococcal antibody concentrations (PCV13) ≥ 0.35 µg/mL and 1.0 µg/mL for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F
  - Anti-rotavirus serum IgA antibody concentrations
  - Anti-rotavirus serum IgA antibody concentrations with ≥3-fold and ≥4-fold rise over baseline
- 30 days after the 12-months vaccinations with M-M-R® II, Prevnar 13®, and Hexacima®:
  - Antibody concentrations/titers for all antigens
  - Anti-pneumococcal antibody concentrations (PCV13) ≥ 0.35 µg / mL and 1.0 µg / mL for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F
  - Anti-measles antibody concentrations (serostatus cutoff 225 mIU / mL)

- Anti-mumps antibody concentrations (serostatus cutoff: 10 Mumps Ab units / mL)
- Anti-rubella antibody (serostatus cutoff: 10 IU / mL)
- Anti-tetanus antibody concentrations ≥ 0.1 IU / mL and 1.0 IU / mL
- Anti-diphtheria antibody concentrations ≥ 0.1 IU / mL and 1.0 IU / mL
- Anti-pertussis (PT and FHA) vaccine response
- Anti-poliovirus types 1, 2, and 3 antibody titers ≥ 1:8
- Anti-PRP antibody concentrations and ≥ 0.15 µg / mL and 1.0 µg / mL
- Anti-HBs concentrations ≥ 10 mIU / mL and 100 mIU / mL

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

Pertussis vaccine response definition:

• If the pre-vaccination concentration is ≥ 4 x LLOQ, then the post-vaccination concentration is >= pre- vaccination concentration

• pre-vaccination concentration is < 4 x LLOQ, then the post-booster vaccination concentration is >= 4 x LLOQ

The following serological endpoints will be described for the Russian Federation (Groups 3 and 4):

- Day 0 (before the first vaccination with Pentaxim®):
  - Anti-pertussis antibody concentrations (PT and FHA)
- 30 days after the 6-months vaccinations with Pentaxim® and ENGERIX-B®:
  - Antibody concentrations/titers for all antigens
  - Anti-tetanus antibody concentrations ≥ 0.1 IU / mL and 1.0 IU / mL
  - Anti-diphtheria antibody concentrations ≥ 0.1 IU / mL and 1.0 IU / mL
  - Anti-pertussis (PT and FHA) vaccine response
  - Anti-poliovirus types 1, 2, and 3 antibody titers ≥ 1:8
  - Anti-PRP antibody concentrations and ≥ 0.15 µg / mL and 1.0 µg / mL
  - Anti-HBs concentrations ≥ 10 mIU / mL and 100 mIU / mL
- 30 days after the 12-months vaccination with MMR:
  - Antibody concentrations for measles, mumps and rubella
  - Anti-measles antibody concentrations (serostatus cutoff 225 mIU / mL)
  - Anti-mumps antibody concentrations (serostatus cutoff: 10 Mumps Ab units / mL)
  - Anti-rubella antibody (serostatus cutoff: 10 IU / mL)

The following serological endpoints will be assessed for Groups 1, 2, and 3:

- D0 (before first vaccination) for Group 1, Group 2, and Group 3:
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers
- 30 days after the 6-month vaccination (after the 2nd dose) with MenACYW conjugate vaccine for Group 1 and Group 3:
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers
  - Titer distribution and reverse cumulative distribution curves (RCDCs)
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers ≥ 1:4 and ≥ 1:8
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers ≥ 4-fold rise from pre-vaccination (D0) to post-vaccination
- 30 days after the 6-month vaccination (after the 3rd dose) with Menveo vaccine for Group 2:
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers
  - Titer distribution and RCDCs
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers ≥ 1:4 and ≥ 1:8
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers ≥ 4-fold rise from pre-vaccination (D0) to post-vaccination

- 30 days after the 12-month vaccination (after the 3rd dose) with MenACYW conjugate vaccine for Group 1 and Group 3:
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers
  - Titer distribution and RCDCs
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers ≥ 1:4 and ≥ 1:8
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers ≥ 4-fold rise from pre-vaccination (D0) to post-vaccination
  - hSBA meningococcal serogroups A, C, Y, and W vaccine seroresponse
- 30 days after the 12-month vaccination (after the 4th dose) with Menveo vaccine for Group 2:
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers
  - Titer distribution and RCDCs
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers ≥ 1:4 and ≥ 1:8
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers ≥ 4-fold rise from pre-vaccination (D0) to post-vaccination
  - hSBA meningococcal serogroups A, C, Y, and W vaccine seroresponse

4) Meningococcal serogroups A, C, Y, and W antibody titers measured by rSBA, before the first vaccination (Visit 1) and 30 days after the last vaccination of the infant series with MenACYW conjugate vaccine or Menveo® (Dose 2 of MenACYW conjugate vaccine and Dose 3 of Menveo®) in Mexico (Group 1 and Group 2);

5) Meningococcal serogroups A, C, Y, and W antibody titers measured by rSBA, before the first vaccination (Visit 1) and 30 days after the last vaccination of the infant series with MenACYW conjugate vaccine (Dose 2 of MenACYW conjugate vaccine) in the Russian Federation (Group 3);

6) Meningococcal serogroups A, C, Y, and W antibody titers measured by rSBA, before the first vaccination (Visit 1) and 30 days after the last vaccination in the second year of life with MenACYW conjugate vaccine or Menveo® in Mexico (Group 1 and Group 2);

7) Meningococcal serogroups A, C, Y, and W antibody titers measured by rSBA before the first vaccination (Visit 1) and 30 days after the last vaccination in the second year of life with MenACYW conjugate vaccine in the Russian Federation (Group 3).

<u>Observational Endpoints</u>

Safety Endpoints

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, relationship to vaccination, and whether the event led to early termination from the study, of any unsolicited systemic AEs reported in the 30 minutes after each vaccination;
- Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and CRF) injection site reactions occurring up to D07 after each vaccination;
- Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and CRF) systemic reactions occurring up to D07 after each vaccination;
- Occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to vaccination, and whether the event led to early termination from the study, of unsolicited AEs up to D30 after each vaccination;

- Occurrence, nature (MedDRA preferred term), time of onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the event led to early termination from the study, of SAEs (including AESIs) throughout the trial from D0 to the last study visit.

Collection of Safety Data

All subjects were followed for safety from Visit 1 to the last study visit.

- All subjects were observed for 30 minutes after vaccination under the supervision of a responsible healthcare professional at each study site and any unsolicited systemic AEs occurring during that time were recorded as immediate unsolicited systemic AEs in the electronic case report form (eCRF).
- The subject's parent / guardian recorded information in a diary card about solicited injection-site reactions and solicited systemic reactions from D0 to D7 after each vaccination and unsolicited AEs were recorded from D0 after each vaccination until the subject returns for the next study visit.
- Serious AEs (including AEs of special interest [AESIs]) were recorded in a diary card throughout the study. The subject's parent / guardian was asked to notify the site immediately about any potential SAEs at any time during the trial.
- A member of the study staff contacted subject's parent / guardian by telephone 8 days (+2 days) after each vaccination visit to identify the occurrence of any SAE (including AESIs) that had not yet been reported and reminded him/her to complete the diary card after each vaccination visit, and to bring it back to the next study visit.
- The completed diary cards were collected and reviewed with the subject's parent / guardian at subsequent visits.

A member of the study staff contacted the subject's parent / guardian by telephone 14 days (+2 days) before the first study visit of the subject's second year of life to identify the occurrence of any SAE that had not yet been reported and reminded him/her to complete the diary card and to next study visit so it could be reviewed at the study site.

Sample size

The sample size of this study was chosen to provide immunogenicity and safety data; it is not intended for the purposes of hypothesis testing. No formal sample size calculation was performed.

Though there are no statistically powered hypotheses, the overall study cohort (n=525) will provide a probability of approximately 95% of observing any AE with a true incidence of 0.57%. The overall MenACYW conjugate vaccine cohort (n=350) will provide a probability of approximately 95% of observing any AE with a true incidence of 0.85%. In treatment arm with n=200, there is a probability of approximately 95% of observing any AE with a true incidence of 1.5%. In treatment arm with n=150, there is a probability of approximately 95% of observing any AE with a true incidence of 2%.

Randomisation and blinding (masking)

Randomisation

On the day of enrollment, subjects who meet the inclusion/exclusion criteria and whose parent / guardian signs the ICF will be randomly assigned in a 2:1 ratio in Mexico, and in a 2:1 ratio in the

Russian Federation such that Group 1 will have 200 subjects, Group 2 will have 100 subjects, Group 3 will have 150 subjects, and Group 4 will have 75 subjects.

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

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

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

Blinding

This trial is open-label; therefore, there is no need for code-breaking procedures. Until database lock and to prevent biases, the laboratory personnel performing the serology testing will be blinded to the group assignment. The laboratory will have a written procedure detailing how the blinding will be maintained.

Changes Following Study Unblinding/Database Lock and Post hoc Analyses:

A post-hoc sensitivity analysis was conducted on the immunogenicity data from Group 3 subjects at 30 days after the last MenACYW conjugate vaccine administration [post-dose 3 at 12 months of age] timepoint. This was due to the identification of unusual immunogenicity results at one of the Group 3 sites in the Russian Federation after conducting the hSBA analysis on the PPAS and FAS. The immune response to Meningococcal A, C, W, and Y serogroups in terms of percentage of subjects with seroprotective antibody titers and GMTs measured by hSBA at site no. 6431007 were more than 10-fold lower compared to the results at other sites in the Russian Federation and in Mexico.

Therefore, immunogenicity results at this site 30 days after last vaccination were excluded in the post-hoc analysis to assess its impact.

Statistical Methods

Data were summarized descriptively. No hypotheses were tested.

Results

Participant flow

A total of 300 subjects were enrolled and randomised in Mexico and 190 subjects were enrolled and randomised in the Russian Federation: 200 subjects were enrolled from Mexico and randomised to Group 1, 100 subjects were enrolled from Mexico and randomised to Group 2, 150 subjects were enrolled from the Russian Federation and randomised to Group 3, and 75 subjects were enrolled from the Russian Federation and randomised to Group 4.

A total of 190 (95.0%) subjects in Group 1 and 92 (92.0%) subjects in Group 2 were present at Visit 6 and completed the study. A total of 18 (6.0%) subjects did not complete the study:

- Fifteen (5.0%) subjects were withdrawn from the study by their parent/guardian (9 [4.5%] subjects in Group 1 and 6 [6.0%] subjects in Group 2);
- Three (1.0%) subjects did not complete the study as they were lost to follow-up (1 [0.5%] subject in Group 1 and 2 [2.0%] subjects in Group 2).

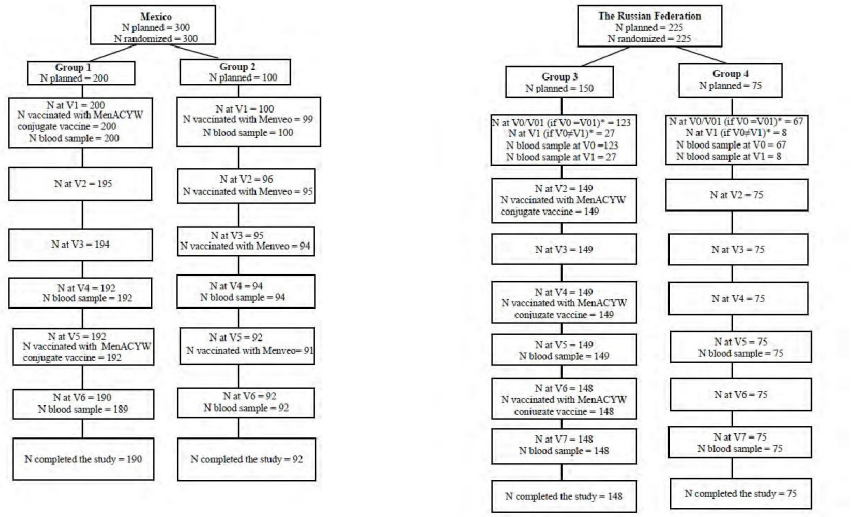
A total of 148 (98.7%) subjects in Group 3 and 75 (100.0%) subjects in Group 4 were present at Visit 7 and completed the study. A total of 2 (0.9%) subjects from Group 3 were withdrawn from the study by their parent/guardian. There were no early terminations in Group 4.

Among all randomised subjects in Mexico (Groups 1 and 2), there were a total of 146 (48.7%) male subjects and 154 (51.3%) female subjects. The overall ratio of male/female subjects was 0.95. The mean age (±SD) of subjects enrolled in Mexico was 67.1 (±7.37) days [range: 60 to 90 days].

Among all randomised subjects in the Russian Federation (Groups 3 and 4), there were a total of 108 (48.0%) male subjects and 117 (52.0%) female subjects. The overall ratio of male/female subjects was 0.92. The mean age (±SD) of subjects enrolled in the Russian Federation was 72.8 (±8.57) days [range: 60 to 93 days].

A summary of disposition/vaccine allocation for randomised subjects is presented in below.

Figure 1: Participant Disposition Flow Chart



N=Total number of subjects enrolled in each study group; V= Visit

*V0 was a screening visit for subjects only in the Russian Federation. If the V0 and V1 did not take place on the same day, V1 could take place up to 5 days after V0.

There were a total of 18 subjects who did not complete the study in Mexico – 15 subjects (from Group 1) were withdrawn from the study by their parent/guardian and 3 subjects (Group 2) were lost to follow-up.

There were 2 subjects from the Russian Federation (Group 3) who were withdrawn from the study by their parent/guardian.

Table 3: Study subjects with early termination by randomised group – randomised study subjects.

	Group 1 (N=200) n (%)	Group 2 (N=100) n (%)	Groups 1 and 2 (N=300) n (%)	Group 3 (N=150) n (%)	Group 4 (N=75) n (%)	Groups 3 and 4 (N=225) n (%)
Completed	190 (95.0)	92 (92.0)	282 (94.0)	148 (98.7)	75 (100)	223 (99.1)
Early termination	10 (5.0)	8 (8.0)	18 (6.0)	2 (1.3)	0	2 (0.9)
Reason						
Adverse Event *	0	0	0	0	0	0
Protocol Deviation	0	0	0	0	0	0
Withdrawal by Parent/Guardian	9 (4.5)	6 (6.0)	15 (5.0)	2 (1.3)	0	2 (0.9)
Lost to Follow-Up	1 (0.5)	2 (2.0)	3 (1.0)	0	0	0

Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 3: MenACYW conjugate vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)
Group 4: Routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation).
n: number of study subjects fulfilling the item listed
*Discontinuations for adverse events may not be considered at the time of the safety analysis if intensity is < Grade 1 according to the Sponsor.

Recruitment

This study was conducted at 11 centres that enrolled participants in The Russian Federation (8 centres) and The United Mexican States (Mexico) (3 centres).

- Study initiation date (first subject, first visit [FSFV]): 17 October 2018
- Study completion date (last subject, last visit [LSLV]): 18 February 2022
- Vaccination period in Mexico: 17 October 2018 to 06 May 2020
- Vaccination period in the Russian Federation: 03 July 2020 to 17January 2022
- Database lock: 23 May 2023

Baseline data

Among all randomised subjects in Mexico (Groups 1 and 2), there were a total of 146 (48.7%) male subjects and 154 (51.3%) female subjects. The overall ratio of male/female subjects was 0.95. The mean age (±SD) of subjects enrolled in Mexico was 67.1 (±7.37) days [range: 60 to 90 days].

Among all randomised subjects in the Russian Federation (Groups 3 and 4), there were a total of 108 (48.0%) male subjects and 117 (52.0%) female subjects. The overall ratio of male/female subjects was 0.92. The mean age (±SD) of subjects enrolled in the Russian Federation was 72.8 (±8.57) days [range: 60 to 93 days].

The distribution of racial origin varied between the 2 countries at enrollment:

- Mexico (Groups 1 and 2): Most of the subjects (81.3%) enrolled were American Indian or of Alaskan Native. The racial origin for the remaining 18.7% subjects was not reported.
- The Russian Federation (Groups 3 and 4): All subjects enrolled were White.

A summary of baseline demographic characteristics by randomised group for all enrolled subjects is presented in the Table below.

Table 4: Baseline demographics by randomised group – randomised study subjects.

	Group 1 (N=200)	Group 2 (N=100)	Groups 1 and 2 (N=300)	Group 3 (N=150)	Group 4 (N=75)	Groups 3 and 4 (N=225)
Sex: n (%)						
Male	100 (50.0)	46 (46.0)	146 (48.7)	81 (54.0)	27 (36.0)	108 (48.0)
Female	100 (50.0)	54 (54.0)	154 (51.3)	69 (46.0)	48 (64.0)	117 (52.0)
Sex ratio: Male/Female	1.00	0.85	0.95	1.17	0.56	0.92
Age (days)						
M	200	100	300	150	75	225
Mean (SD)	66.9 (7.30)	67.6 (7.52)	67.1 (7.37)	73.1 (8.53)	72.1 (8.69)	72.8 (8.57)
Min ; Max	60.0 ; 89.0	60.0 ; 90.0	60.0 ; 90.0	60.0 ; 93.0	61.0 ; 90.0	60.0 ; 93.0
Median	64.0	65.0	64.0	71.5	70.0	70.0
Q1 ; Q3	62.0 ; 69.0	62.0 ; 70.0	62.0 ; 69.0	66.0 ; 79.0	65.0 ; 80.0	66.0 ; 79.0
Racial origin: n (%)						
White	0	0	0	150 (100)	75 (100)	225 (100)
Asian	0	0	0	0	0	0
Black or African American	0	0	0	0	0	0
American Indian or Alaska Native	166 (83.0)	78 (78.0)	244 (81.3)	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
Mixed Origin	0	0	0	0	0	0
Not Reported	34 (17.0)	22 (22.0)	56 (18.7)	0	0	0
Unknown	0	0	0	0	0	0
Ethnicity: n (%)						
Hispanic or Latino	199 (99.5)	99 (99.0)	298 (99.3)	0	1 (1.3)	1 (0.4)
Not Hispanic or Latino	0	0	0	146 (97.3)	72 (96.0)	218 (96.9)
Not Reported	1 (0.5)	1 (1.0)	2 (0.7)	3 (2.0)	2 (2.7)	5 (2.2)
Unknown	0	0	0	1 (0.7)	0	1 (0.4)

n: number of subjects fulfilling the item listed in the first column
M: number of subjects with available data for the relevant endpoint; Percentages are based on M.
N: number of subjects randomized in each study group
Q1; Q3: first quartile; third quartile; SD: standard deviation
Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 3: MenACYW conjugate vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)
Group 4: Routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)

Number analysed

Immunogenicity

Table 5: Immunogenicity Analysis Sets by randomised group for infant vaccination – Randomised study subjects.

	Group 1 (N=200) n (%)	Group 2 (N=100) n (%)	Groups 1 and 2 (N=300) n (%)	Group 3 (N=150) n (%)	Group 4 (N=75) n (%)	Groups 3 and 4 (N=225) n (%)
Full Analysis Set 1	192 (96.0)	94 (94.0)	286 (95.3)	148 (98.7)	75 (100)	223 (99.1)
Not injected	0	0	0	0	0	0
Post-vaccination blood sample did not produce valid result *	8 (4.0)	6 (6.0)	14 (4.7)	2 (1.3)	0	2 (0.9)
Per-Protocol Analysis Set 1	176 (88.0)	81 (81.0)	257 (85.7)	97 (64.7)	53 (70.7)	150 (66.7)
Subjects with at least one criterion for exclusion from PPAS1	24 (12.0)	19 (19.0)	43 (14.3)	53 (35.3)	22 (29.3)	75 (33.3)
Did not meet all protocol-specified inclusion/exclusion criteria	2 (1.0)	1 (1.0)	3 (1.0)	2 (1.3)	1 (1.3)	3 (1.3)
Did not complete the vaccination schedule of the infant series	5 (2.5)	5 (5.0)	10 (3.3)	1 (0.7)	0	1 (0.4)
Received vaccine other than randomized	0	0	0	0	0	0
Vaccine not prepared/administered as per protocol	0	0	0	0	0	0
Did not receive vaccine in proper time window	12 (6.0)	10 (10.0)	22 (7.3)	49 (32.7)	20 (26.7)	69 (30.7)
Did not provide a post-dose serology sample or not in time window	3 (1.5)	2 (2.0)	5 (1.7)	1 (0.7)	1 (1.3)	2 (0.9)
Received protocol-restricted therapy/medication/vaccine	2 (1.0)	1 (1.0)	3 (1.0)	0	0	0
Post-dose serology sample did not produce a valid test result *	0	0	0	0	0	0

n: number of subjects fulfilling the item listed. *: i.e. results equal to 'NR' or missing for all antigens (at post-vaccination)
FAS1: Full analysis set for infant vaccination; PPAS1: Per-protocol analysis set for infant vaccination
Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 3: MenACYW conjugate vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)
Group 4: Routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)
Note: A subject may be associated with more than 1 criterion. Subjects with more than 1 criterion are counted only once and are classified in the category of criterion listed first in this table.

Table 6: Immunogenicity Analysis Sets by randomised group for second year of life vaccination – Randomised study subjects.

	Group 1 (N=200) n (%)	Group 2 (N=100) n (%)	Groups 1 and 2 (N=300) n (%)	Group 3 (N=150) n (%)	Group 4 (N=75) n (%)	Groups 3 and 4 (N=225) n (%)
Full Analysis Set 2	189 (94.5)	92 (92.0)	281 (93.7)	148 (98.7)	75 (100)	223 (99.1)
Not injected	8 (4.0)	8 (8.0)	16 (5.3)	2 (1.3)	0	2 (0.9)
Post-vaccination blood sample did not produce valid result *	11 (5.5)	8 (8.0)	19 (6.3)	2 (1.3)	0	2 (0.9)
Per-Protocol Analysis Set 2	126 (63.0)	60 (60.0)	186 (62.0)	96 (64.0)	50 (66.7)	146 (64.9)
Subjects with at least one criterion for exclusion from PPAS2	74 (37.0)	40 (40.0)	114 (38.0)	54 (36.0)	25 (33.3)	79 (35.1)
Did not meet all protocol-specified inclusion/exclusion criteria	2 (1.0)	1 (1.0)	3 (1.0)	2 (1.3)	1 (1.3)	3 (1.3)
Did not complete the vaccination schedule during both infant and second year of life	9 (4.5)	9 (9.0)	18 (6.0)	2 (1.3)	0	2 (0.9)
Received vaccine other than randomized during both infant and second year of life	0	0	0	0	0	0
Vaccine not prepared/administered as per protocol during both infant and second year of life	0	0	0	1 (0.7)	0	1 (0.4)
Did not receive vaccine in proper time window in the second year of life	52 (26.0)	28 (28.0)	80 (26.7)	46 (30.7)	20 (26.7)	66 (29.3)
Did not provide a post-dose serology sample or not in time window in the second year of life	5 (2.5)	1 (1.0)	6 (2.0)	3 (2.0)	4 (5.3)	7 (3.1)
Received protocol-restricted therapy/medication/vaccine in the second year of life	6 (3.0)	1 (1.0)	7 (2.3)	0	0	0
Post-dose serology sample did not produce a valid test result in the second year of life *	0	0	0	0	0	0

n: number of subjects fulfilling the item listed. *: i.e. results equal to 'NR' or missing for all antigens (at post-vaccination)
Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico); Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico); Group 3: MenACYW conjugate vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation); Group 4: Routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)
Note: A subject may be associated with more than 1 criterion. Subjects with more than 1 criterion are counted only once and are classified in the category of criterion listed first in this table.

Safety

All safety analyses were performed on the Safety Analysis Sets (SafAS and SafAS1 – SafAS6; Table below).

Table 7: Safety Analysis Sets by vaccination group – Randomised study subjects.

	Group 1 (N=200) n (%)	Group 2 (N=100) n (%)	Groups 1 and 2 (N=300) n (%)	Group 3 (N=150) n (%)	Group 4 (N=75) n (%)	Groups 3 and 4 (N=225) n (%)
Subjects received vaccine	200 (100)	100 (100)	300 (100)	150 (100)	75 (100)	225 (100)
Overall Safety Analysis Set for Any Dose	200 (100)	100 (100)	300 (100)	150 (100)	75 (100)	225 (100)
Safety Analysis Set 1 for Vaccination at 2 Months of Age	200 (100)	100 (100)	300 (100)	150 (100)	75 (100)	225 (100)
Safety Analysis Set 2 for Vaccination at 3 Months of Age for Russia Only	NA	NA	NA	149 (99.3)	75 (100)	224 (99.6)
Safety Analysis Set 3 for Vaccination at 4 Months of Age for Mexico Only	195 (97.5)	96 (96.0)	291 (97.0)	NA	NA	NA
Safety Analysis Set 4 for Vaccination at 4.5 Months of Age for Russia Only	NA	NA	NA	149 (99.3)	75 (100)	224 (99.6)
Safety Analysis Set 5 for Vaccination at 6 Months of Age	194 (97.0)	95 (95.0)	289 (96.3)	149 (99.3)	75 (100)	224 (99.6)
Safety Analysis Set 6 for Vaccination at 12 Months of Age	192 (96.0)	92 (92.0)	284 (94.7)	148 (98.7)	75 (100)	223 (99.1)

n: number of subjects experiencing the endpoint; NA: not applicable
"Subjects received vaccine" is defined as subjects who received at least one dose of study vaccines, including MenACYW conjugate vaccine, Menveo® and the concomitant vaccines.
"Safety analysis set" is defined as subjects who received at least one dose of study vaccines and for whom any safety data are available.
Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 3: MenACYW conjugate vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)
Group 4: Routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)

Exposure

Mexico:

Three doses of MenACYW conjugate vaccine were administered during the study:

A pre-vaccination blood sample was provided at Visit 1 by 200 (100.0%) subjects in Group 1 and 100 (100.0%) subjects in Group 2.

- 200 (100.0%) subjects randomised in Group 1 and 1 (1.0%) subject randomised in Group 2 were administered MenACYW conjugate vaccine at Visit 1 (2 months of age);
- 194 (97.0%) subjects randomised in Group 1 were administered MenACYW conjugate vaccine at Visit 3 (6 months of age);
- 192 (96.0%) subjects randomised in Group 1 and 1 (1.0%) subject randomised in Group 2 were administered MenACYW conjugate vaccine at Visit 5 (12 months of age);

A post-vaccination blood sample was provided at Visit 4 (7 months of age) by 192 (96.0%) subjects in Group 1 and 94 (94.0%) subjects in Group 2 and at Visit 6 (13 months of age) by 189 (94.5%) subjects in Group 1 and 92 (92.0%) subjects in Group 2.

The Russian Federation:

Three doses of MenACYW conjugate vaccine were administered during the study:

A pre-vaccination blood sample was provided at Visit 0 (screening visit) by 123 (82.0%) subjects in Group 3 and 67 (89.3%) subjects in Group 4 and at Visit 1 by 27 (18.0%) subjects in Group 3 and 8 (10.7%) subjects in Group 4.

- 149 (99.3%) subjects randomised in Group 3 were administered MenACYW conjugate vaccine at Visit 2 (3 months of age)
- 149 (99.3%) subjects randomised in Group 3 were administered MenACYW conjugate vaccine at Visit 4 (6 months of age)
- 148 (98.7%) subjects randomised in Group 3 were administered MenACYW conjugate vaccine at Visit 6 (12 months of age)

A post-vaccination blood sample was provided at Visit 5 (7 months of age) by 149 (99.3%) subjects in Group 3 and 75 (100.0%) subjects in Group 4 and at Visit 7 (13 months of age) by 148 (98.7%) subjects in Group 3 and 75 (100.0%) subjects in Group 4.

Efficacy results

1. Primary objective

Meningococcal hSBA Seroprotection rates (antibody titer ≥ 1:8) in Mexico and the Russian Federation after last vaccination in the second year of life

Table 8: Number and percentage of subjects with hSBA titer ≥ 1:8 – 30 days after the last vaccination in the second year of life – Per-Protocol Analysis Set 2

		Group 1 (N=126)			Group 2 (N=60)			Group 3 (N=96)		
Serogroup	**Time Point**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
A	D30	123/126	97.6	(93.2 ; 99.5)	57/60	95.0	(86.1 ; 99.0)	86/96	89.6	(81.7 ; 94.9)
C	D30	125/126	99.2	(95.7 ; 100)	56/60	93.3	(83.8 ; 98.2)	79/96	82.3	(73.2 ; 89.3)
Y	D30	125/125	100	(97.1 ; 100)	60/60	100	(94.0 ; 100)	77/96	80.2	(70.8 ; 87.6)
W	D30	125/125	100	(97.1 ; 100)	60/60	100	(94.0 ; 100)	77/96	80.2	(70.8 ; 87.6)

n: number of subjects with titers that meet the hSBA titer >= 1:8 criteria
M: number of subjects with valid serology results for the particular serogroup and time point
N: number of subjects in Per-Protocol Analysis Set 2
Percentages are based on M.
Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 3: MenACYW conjugate vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)

Sensitivity Post hoc Analysis

A post-hoc sensitivity analysis was conducted on the immunogenicity data from Group 3 subjects at 30 days after the last MenACYW conjugate vaccine administration [post-dose 3 at 12 months of age] timepoint. This was due to the identification of unusual immunogenicity results at one of the Group 3 sites in the Russian Federation after conducting the hSBA analysis on the PPAS and FAS. The immune response to Meningococcal A, C, W, and Y serogroups in terms of percentage of subjects with seroprotective antibody titers and GMTs

measured by hSBA at site no. 6431007 were more than 10-fold lower compared to the results at other sites in the Russian Federation and in Mexico.

The table below presents the number and percentage of subjects with hSBA titers ≥ 1:8 (without Russian Federation site 6431007) 30 days after the last vaccination in the second year of life for subjects in PPAS2.

Table 9: Number and percentage of subjects with hSBA titer ≥ 1:8 – 30 days after the last vaccination in the second year of life – Per-Protocol Analysis Set 2 – without the Russian Federation site 6431007

		Group 1 (N=126)			Group 2 (N=60)			Group 3* (N=64)		
Serogroup	**Time Point**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
A	D30	123/126	97.6	(93.2 ; 99.5)	57/60	95.0	(86.1 ; 99.0)	61/64	95.3	(86.9 ; 99.0)
C	D30	125/126	99.2	(95.7 ; 100)	56/60	93.3	(83.8 ; 98.2)	62/64	96.9	(89.2 ; 99.6)
Y	D30	125/125	100	(97.1 ; 100)	60/60	100	(94.0 ; 100)	61/64	95.3	(86.9 ; 99.0)
W	D30	125/125	100	(97.1 ; 100)	60/60	100	(94.0 ; 100)	60/64	93.8	(84.8 ; 98.3)

*Subjects from Group 3 without Russian site 6431007
n: number of subjects with titers that meet the hSBA titer >= 1:8 criteria
M: number of subjects with valid serology results for the particular serogroup and time point
N: number of subjects in Per-Protocol Analysis Set 2
Percentages are based on M.
Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 3: MenACYW conjugate vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)

2. Secondary objectives

Seroresponse of Antibody Titers against Meningococcal Serogroups A, C, Y, and W

Table 10: Number and percentage of subjects with hSBA vaccine seroresponse 30 days after the last vaccination in infant series – Per-Protocol Analysis Set 1

		Group 1 (N=176)			Group 2 (N=81)			Group 3 (N=97)		
Serogroup	**Baseline Status**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
A	Any	149/176	84.7	(78.5 ; 89.6)	47/81	58.0	(46.5 ; 68.9)	68/97	70.1	(60.0 ; 79.0)
	S-	144/167	86.2	(80.1 ; 91.1)	47/80	58.8	(47.2 ; 69.6)	65/92	70.7	(60.2 ; 79.7)
	S+	5/9	55.6	(21.2 ; 86.3)	0/1	0	(0 ; 97.5)	3/5	60.0	(14.7 ; 94.7)
C	Any	176/176	100	(97.9 ; 100)	70/81	86.4	(77.0 ; 93.0)	92/97	94.8	(88.4 ; 98.3)
	S-	175/175	100	(97.9 ; 100)	68/78	87.2	(77.7 ; 93.7)	90/95	94.7	(88.1 ; 98.3)
	S+	1/1	100	(2.5 ; 100)	2/3	66.7	(9.4 ; 99.2)	2/2	100	(15.8 ; 100)
Y	Any	175/176	99.4	(96.9 ; 100)	75/81	92.6	(84.6 ; 97.2)	85/97	87.6	(79.4 ; 93.4)
	S-	167/168	99.4	(96.7 ; 100)	73/75	97.3	(90.7 ; 99.7)	82/92	89.1	(80.9 ; 94.7)
	S+	8/8	100	(63.1 ; 100)	2/6	33.3	(4.3 ; 77.7)	3/5	60.0	(14.7 ; 94.7)
W	Any	173/176	98.3	(95.1 ; 99.6)	79/81	97.5	(91.4 ; 99.7)	91/97	93.8	(87.0 ; 97.7)
	S-	147/147	100	(97.5 ; 100)	72/73	98.6	(92.6 ; 100)	88/94	93.6	(86.6 ; 97.6)
	S+	26/29	89.7	(72.6 ; 97.8)	7/8	87.5	(47.3 ; 99.7)	3/3	100	(29.2 ; 100)

n: number of subjects with titers that meet the hSBA vaccine seroresponse criteria; M: number of subjects with valid serology results for the particular serogroup
N: number of subjects in Per-Protocol Analysis Set 1; Percentages are based on M.
hSBA vaccine seroresponse: for a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be >= 1:16; for a subject with a pre-vaccination titer >= 1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer.
S-: Pre-vaccination baseline titer is < 1:8; S+: Pre-vaccination baseline titer is >= 1:8
Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 3: MenACYW conjugate vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)

Table 11: Number and percentage of subjects with hSBA vaccine seroresponse 30 days after the last vaccination in the second year of life - Per-Protocol Analysis Set 2

		Group 1 (N=126)			Group 2 (N=60)			Group 3 (N=96)		
Serogroup	**Baseline Status**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
A	Any	122/126	96.8	(92.1 ; 99.1)	51/60	85.0	(73.4 ; 92.9)	71/96	74.0	(64.0 ; 82.4)
	S-	116/118	98.3	(94.0 ; 99.8)	51/59	86.4	(75.0 ; 94.0)	65/89	73.0	(62.6 ; 81.9)
	S+	6/8	75.0	(34.9 ; 96.8)	0/1	0	(0 ; 97.5)	6/7	85.7	(42.1 ; 99.6)
C	Any	125/126	99.2	(95.7 ; 100)	53/60	88.3	(77.4 ; 95.2)	78/96	81.3	(72.0 ; 88.5)
	S-	125/126	99.2	(95.7 ; 100)	50/57	87.7	(76.3 ; 94.9)	76/94	80.9	(71.4 ; 88.2)
	S+	0/0	NC	(NC ; NC)	3/3	100	(29.2 ; 100)	2/2	100	(15.8 ; 100)
Y	Any	125/125	100	(97.1 ; 100)	58/60	96.7	(88.5 ; 99.6)	77/96	80.2	(70.8 ; 87.6)
	S-	121/121	100	(97.0 ; 100)	55/55	100	(93.5 ; 100)	75/93	80.6	(71.1 ; 88.1)
	S+	4/4	100	(39.8 ; 100)	3/5	60.0	(14.7 ; 94.7)	2/3	66.7	(9.4 ; 99.2)
W	Any	124/125	99.2	(95.6 ; 100)	60/60	100	(94.0 ; 100)	76/96	79.2	(69.7 ; 86.8)
	S-	105/105	100	(96.5 ; 100)	55/55	100	(93.5 ; 100)	76/95	80.0	(70.5 ; 87.5)
	S+	19/20	95.0	(75.1 ; 99.9)	5/5	100	(47.8 ; 100)	0/1	0	(0 ; 97.5)

n: number of subjects with titers that meet the hSBA vaccine seroresponse criteria; M: number of subjects with valid serology results for the particular serogroup
N: number of subjects in Per-Protocol Analysis Set 2; Percentages are based on M.
hSBA vaccine seroresponse: for a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be >= 1:16; for a subject with a pre-vaccination titer >= 1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer.
S-: Pre-vaccination baseline titer is < 1:8; S+: Pre-vaccination baseline titer is >= 1:8
Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 3: MenACYW conjugate vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)

Sensitivity Post hoc Analysis

Table 12: Number and percentage of subjects with hSBA vaccine seroresponse 30 days after the last vaccination in the second year of life - PPAS 2 – without Russian site 6431007

		Group 1 (N=126)			Group 2 (N=60)			Group 3* (N=64)		
Serogroup	**Baseline Status**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
A	Any	122/126	96.8	(92.1 ; 99.1)	51/60	85.0	(73.4 ; 92.9)	60/64	93.8	(84.8 ; 98.3)
	S-	116/118	98.3	(94.0 ; 99.8)	51/59	86.4	(75.0 ; 94.0)	54/58	93.1	(83.3 ; 98.1)
	S+	6/8	75.0	(34.9 ; 96.8)	0/1	0	(0 ; 97.5)	6/6	100	(54.1 ; 100)
C	Any	125/126	99.2	(95.7 ; 100)	53/60	88.3	(77.4 ; 95.2)	62/64	96.9	(89.2 ; 99.6)
	S-	125/126	99.2	(95.7 ; 100)	50/57	87.7	(76.3 ; 94.9)	60/62	96.8	(88.8 ; 99.6)
	S+	0/0	NC	(NC ; NC)	3/3	100	(29.2 ; 100)	2/2	100	(15.8 ; 100)
Y	Any	125/125	100	(97.1 ; 100)	58/60	96.7	(88.5 ; 99.6)	61/64	95.3	(86.9 ; 99.0)
	S-	121/121	100	(97.0 ; 100)	55/55	100	(93.5 ; 100)	59/61	96.7	(88.7 ; 99.6)
	S+	4/4	100	(39.8 ; 100)	3/5	60.0	(14.7 ; 94.7)	2/3	66.7	(9.4 ; 99.2)
W	Any	124/125	99.2	(95.6 ; 100)	60/60	100	(94.0 ; 100)	60/64	93.8	(84.8 ; 98.3)
	S-	105/105	100	(96.5 ; 100)	55/55	100	(93.5 ; 100)	60/64	93.8	(84.8 ; 98.3)
	S+	19/20	95.0	(75.1 ; 99.9)	5/5	100	(47.8 ; 100)	0/0	NC	(NC ; NC)

*Subjects from Group 3 without Russian site 6431007
n: number of subjects with titers that meet the hSBA vaccine seroresponse criteria; M: number of subjects with valid serology results for the particular serogroup
N: number of subjects in Per-Protocol Analysis Set 2; Percentages are based on M.; NC: not computed
hSBA vaccine seroresponse: for a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be >= 1:16; for a subject with a pre-vaccination titer >= 1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer. S-: Pre-vaccination baseline titer is < 1:8; S+: Pre-vaccination baseline titer is >= 1:8
Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 3: MenACYW conjugate vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)

hSBA Geometric Mean Titers of Antibodies against Meningococcal Serogroups A, C, Y, and W

Table 13: Summary of geometric means of hSBA titers before the first vaccination and 30 days after the last vaccination of the infant series – PPAS 1

		Group 1 (N=176)			Group 2 (N=81)			Group 3 (N=97)		
Serogroup	**Time Point**	**M**	**GMT**	**(95% CI)**	**M**	**GMT**	**(95% CI)**	**M**	**GMT**	**(95% CI)**
A	D0	176	2.65	(2.39 ; 2.93)	81	2.24	(2.10 ; 2.38)	97	2.88	(2.64 ; 3.14)
	D30	176	71.7	(56.8 ; 90.7)	81	16.7	(12.0 ; 23.3)	97	31.5	(22.2 ; 44.9)
C	D0	176	2.16	(2.08 ; 2.23)	81	2.29	(2.13 ; 2.47)	97	2.16	(2.04 ; 2.30)
	D30	176	626	(549 ; 714)	81	62.4	(47.2 ; 82.4)	97	267	(196 ; 365)
Y	D0	176	2.62	(2.45 ; 2.81)	81	2.89	(2.51 ; 3.33)	97	2.37	(2.07 ; 2.72)
	D30	176	246	(216 ; 281)	81	59.8	(46.9 ; 76.1)	97	78.2	(60.3 ; 101)
W	D0	176	3.57	(3.21 ; 3.97)	81	3.15	(2.79 ; 3.55)	97	2.18	(2.04 ; 2.32)
	D30	176	340	(294 ; 393)	81	95.7	(78.4 ; 117)	97	78.7	(61.9 ; 100)

M: number of subjects with valid serology results for the particular serogroup and time point
N: number of subjects in Per-Protocol Analysis Set 1
Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 3: MenACYW conjugate vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)

Table 14: Summary of geometric means of hSBA titers 30 days after the last vaccination in the second year of life – PPAS 2

		Group 1 (N=126)			Group 2 (N=60)			Group 3 (N=96)		
Serogroup	**Time Point**	**M**	**GMT**	**(95% CI)**	**M**	**GMT**	**(95% CI)**	**M**	**GMT**	**(95% CI)**
A	D30	126	145	(114 ; 185)	60	65.5	(44.5 ; 96.3)	96	85.4	(54.0 ; 135)
C	D30	126	897	(742 ; 1086)	60	77.0	(52.5 ; 113)	96	214	(130 ; 353)
Y	D30	125	401	(343 ; 469)	60	228	(173 ; 301)	96	97.3	(63.4 ; 149)
W	D30	125	639	(542 ; 754)	60	242	(184 ; 318)	96	123	(77.1 ; 195)

M: number of subjects with valid serology results for the particular serogroup and time point
N: number of subjects in Per-Protocol Analysis Set 2
Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 3: MenACYW conjugate vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)

Sensitivity Post hoc Analysis

Table 15: Summary of geometric means of hSBA titers 30 days after the last vaccination in the second year of life – PPAS 2 – without Russian site 6431007

		Group 1 (N=126)			Group 2 (N=60)			Group 3* (N=64)		
Serogroup	**Time Point**	**M**	**GMT**	**(95% CI)**	**M**	**GMT**	**(95% CI)**	**M**	**GMT**	**(95% CI)**
A	D30	126	145	(114 ; 185)	60	65.5	(44.5 ; 96.3)	64	264	(164 ; 425)
C	D30	126	897	(742 ; 1086)	60	77.0	(52.5 ; 113)	64	732	(476 ; 1126)
Y	D30	125	401	(343 ; 469)	60	228	(173 ; 301)	64	227	(156 ; 332)
W	D30	125	639	(542 ; 754)	60	242	(184 ; 318)	64	285	(181 ; 449)

*Subjects from Group 3 without Russian site 6431007
M: number of subjects with valid serology results for the particular serogroup and time point
N: number of subjects in Per-Protocol Analysis Set 2
Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 3: MenACYW conjugate vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)

Distribution of hSBA Titers and Reverse Cumulative Distribution Curves of Meningococcal Antibody Titers

Distribution of hSBA Titers and RCDCs at D0 and D30 after the last vaccination of the infant series

Mexico

An immune response against meningococcal serogroups A, C, Y, and W was observed at D30 after the last vaccination in the infant series. At D30, the antibody titers of Group 1 were shifted to the right compared to Group 2 for all serogroups indicating a stronger immune response with MenACYW conjugate vaccine than with Menveo vaccine.

The Russian Federation

An immune response against meningococcal serogroups A, C, Y, and W was observed at D30 after the last vaccination in the infant series. At D30, the antibody titers were shifted to the right compared to D0 for all serogroups.

Distribution of hSBA Titers and RCDCs at D30 after the last vaccination in the second year of life

Mexico

An immune response against meningococcal serogroups A, C, Y, and W was observed at D30 after the last vaccination in the second year of life. At D30, the antibody distribution titers of Group 1 were shifted to the right compared to Group 2 for all serogroups indicating a stronger immune response with MenACYW conjugate vaccine than with Menveo vaccine.

The Russian Federation

An immune response against meningococcal serogroups A, C, Y, and W was observed at D30 after the last vaccination in the second year of life. At D30, the antibody titers were shifted to the right compared to D0.

Four-Fold Rise in hSBA Antibody Titers

Table 16: Number and percentage of subjects with >= 4-fold rise of hSBA titers from pre-vaccination to 30 days after the last vaccination of the infant series – PPAS 1

	Group 1 (N=176)			Group 2 (N=81)			Group 3 (N=97)		
Serogroup	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
A	149/176	84.7	(78.5 ; 89.6)	47/81	58.0	(46.5 ; 68.9)	68/97	70.1	(60.0 ; 79.0)
C	176/176	100	(97.9 ; 100)	70/81	86.4	(77.0 ; 93.0)	92/97	94.8	(88.4 ; 98.3)
Y	175/176	99.4	(96.9 ; 100)	75/81	92.6	(84.6 ; 97.2)	85/97	87.6	(79.4 ; 93.4)
W	173/176	98.3	(95.1 ; 99.6)	79/81	97.5	(91.4 ; 99.7)	91/97	93.8	(87.0 ; 97.7)

n: number of subjects with titers that meets the fold rise criteria
M: number of subjects with valid serology results for the particular serogroup
N: number of subjects in Per-Protocol Analysis Set 1
Percentages are based on M.
Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 3: MenACYW conjugate vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)

Table 17: Number and percentage of subjects with >= 4-fold rise of hSBA titers from pre-vaccination to 30 days after the last vaccination in the second year of life – PPAS 2

	Group 1 (N=126)			Group 2 (N=60)			Group 3 (N=96)		
Serogroup	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
A	122/126	96.8	(92.1 ; 99.1)	51/60	85.0	(73.4 ; 92.9)	71/96	74.0	(64.0 ; 82.4)
C	125/126	99.2	(95.7 ; 100)	53/60	88.3	(77.4 ; 95.2)	78/96	81.3	(72.0 ; 88.5)
Y	125/125	100	(97.1 ; 100)	58/60	96.7	(88.5 ; 99.6)	77/96	80.2	(70.8 ; 87.6)
W	124/125	99.2	(95.6 ; 100)	60/60	100	(94.0 ; 100)	76/96	79.2	(69.7 ; 86.8)

N: number of subjects with titers that meets the fold rise criteria
M: number of subjects with valid serology results for the particular serogroup
N: number of subjects in Per-Protocol Analysis Set 2
Percentages are based on M.
Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 3: MenACYW conjugate vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)

Sensitivity Post hoc Analysis

Table 18: Number and percentage of subjects with >= 4-fold rise of hSBA titers from pre-vaccination to 30 days after the last vaccination in the second year of life – PPAS 2 – without Russian site 6431007

	Group 1 (N=126)			Group 2 (N=60)			Group 3* (N=64)		
Serogroup	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
A	122/126	96.8	(92.1 ; 99.1)	51/60	85.0	(73.4 ; 92.9)	60/64	93.8	(84.8 ; 98.3)
C	125/126	99.2	(95.7 ; 100)	53/60	88.3	(77.4 ; 95.2)	62/64	96.9	(89.2 ; 99.6)
Y	125/125	100	(97.1 ; 100)	58/60	96.7	(88.5 ; 99.6)	61/64	95.3	(86.9 ; 99.0)
W	124/125	99.2	(95.6 ; 100)	60/60	100	(94.0 ; 100)	60/64	93.8	(84.8 ; 98.3)

*Subjects from Group 3 without Russian site 6431007
n: number of subjects with titers that meets the fold rise criteria
M: number of subjects with valid serology results for the particular serogroup
N: number of subjects in Per-Protocol Analysis Set 2
Percentages are based on M.
Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 3: MenACYW conjugate vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)

Immunogenicity profiles of Routine Paediatric Vaccines When Administered Concomitantly with a Meningococcal Vaccine or When Administered Alone

Mexico

Prevnar 13 Vaccine

Table 19: Summary of response rates for Prevenar 13 vaccine 30 days after the last vaccination in infant series in Mexico – PPAS 1

		Group 1 (N=176)			Group 2 (N=81)		
Serotype	**Criteria**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
1	>=0.35 ug/mL	175/175	100	(97.9 ; 100)	81/81	100	(95.5 ; 100)
	>=1.0 ug/mL	167/175	95.4	(91.2 ; 98.0)	77/81	95.1	(87.8 ; 98.6)
3	>=0.35 ug/mL	143/175	81.7	(75.2 ; 87.1)	60/81	74.1	(63.1 ; 83.2)
	>=1.0 ug/mL	35/175	20.0	(14.3 ; 26.7)	12/81	14.8	(7.9 ; 24.4)
4	>=0.35 ug/mL	174/175	99.4	(96.9 ; 100)	80/81	98.8	(93.3 ; 100)
	>=1.0 ug/mL	147/175	84.0	(77.7 ; 89.1)	64/81	79.0	(68.5 ; 87.3)
5	>=0.35 ug/mL	174/175	99.4	(96.9 ; 100)	81/81	100	(95.5 ; 100)
	>=1.0 ug/mL	155/175	88.6	(82.9 ; 92.9)	66/81	81.5	(71.3 ; 89.2)
6A	>=0.35 ug/mL	175/175	100	(97.9 ; 100)	81/81	100	(95.5 ; 100)
	>=1.0 ug/mL	169/175	96.6	(92.7 ; 98.7)	78/81	96.3	(89.6 ; 99.2)
6B	>=0.35 ug/mL	171/175	97.7	(94.3 ; 99.4)	80/81	98.8	(93.3 ; 100)
	>=1.0 ug/mL	155/175	88.6	(82.9 ; 92.9)	66/81	81.5	(71.3 ; 89.2)
7F	>=0.35 ug/mL	175/175	100	(97.9 ; 100)	81/81	100	(95.5 ; 100)
	>=1.0 ug/mL	174/175	99.4	(96.9 ; 100)	81/81	100	(95.5 ; 100)
9V	>=0.35 ug/mL	175/175	100	(97.9 ; 100)	81/81	100	(95.5 ; 100)
	>=1.0 ug/mL	152/175	86.9	(80.9 ; 91.5)	69/81	85.2	(75.6 ; 92.1)
14	>=0.35 ug/mL	174/174	100	(97.9 ; 100)	81/81	100	(95.5 ; 100)
	>=1.0 ug/mL	172/174	98.9	(95.9 ; 99.9)	81/81	100	(95.5 ; 100)
18C	>=0.35 ug/mL	175/175	100	(97.9 ; 100)	79/81	97.5	(91.4 ; 99.7)
	>=1.0 ug/mL	159/175	90.9	(85.6 ; 94.7)	66/81	81.5	(71.3 ; 89.2)
19A	>=0.35 ug/mL	174/175	99.4	(96.9 ; 100)	81/81	100	(95.5 ; 100)
	>=1.0 ug/mL	152/175	86.9	(80.9 ; 91.5)	68/81	84.0	(74.1 ; 91.2)
19F	>=0.35 ug/mL	174/175	99.4	(96.9 ; 100)	80/81	98.8	(93.3 ; 100)
	>=1.0 ug/mL	171/175	97.7	(94.3 ; 99.4)	80/81	98.8	(93.3 ; 100)
23F	>=0.35 ug/mL	168/175	96.0	(91.9 ; 98.4)	78/81	96.3	(89.6 ; 99.2)
	>=1.0 ug/mL	142/175	81.1	(74.5 ; 86.6)	64/81	79.0	(68.5 ; 87.3)

n: number of subjects experiencing the endpoint listed in the first two columns
M: number of subjects with valid serology results for the particular pneumococcal serotype
N: number of subjects in Per-Protocol Analysis Set 1
Percentages are based on M.
Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)

Table 20: Summary of response rates for Prevenar 13 vaccine 30 days after the last vaccination in the second year of life in Mexico – PPAS 2

		Group 1 (N=126)			Group 2 (N=60)		
Serotype	**Criteria**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
1	>=0.35 ug/mL	122/125	97.6	(93.1 ; 99.5)	59/60	98.3	(91.1 ; 100)
	>=1.0 ug/mL	105/125	84.0	(76.4 ; 89.9)	48/60	80.0	(67.7 ; 89.2)
3	>=0.35 ug/mL	86/125	68.8	(59.9 ; 76.8)	40/60	66.7	(53.3 ; 78.3)
	>=1.0 ug/mL	25/125	20.0	(13.4 ; 28.1)	15/60	25.0	(14.7 ; 37.9)
4	>=0.35 ug/mL	113/125	90.4	(83.8 ; 94.9)	52/60	86.7	(75.4 ; 94.1)
	>=1.0 ug/mL	90/125	72.0	(63.3 ; 79.7)	39/60	65.0	(51.6 ; 76.9)
5	>=0.35 ug/mL	119/125	95.2	(89.8 ; 98.2)	58/60	96.7	(88.5 ; 99.6)
	>=1.0 ug/mL	106/125	84.8	(77.3 ; 90.6)	49/60	81.7	(69.6 ; 90.5)
6A	>=0.35 ug/mL	123/125	98.4	(94.3 ; 99.8)	60/60	100	(94.0 ; 100)
	>=1.0 ug/mL	113/125	90.4	(83.8 ; 94.9)	52/60	86.7	(75.4 ; 94.1)
6B	>=0.35 ug/mL	119/125	95.2	(89.8 ; 98.2)	56/60	93.3	(83.8 ; 98.2)
	>=1.0 ug/mL	111/125	88.8	(81.9 ; 93.7)	52/60	86.7	(75.4 ; 94.1)
7F	>=0.35 ug/mL	124/125	99.2	(95.6 ; 100)	60/60	100	(94.0 ; 100)
	>=1.0 ug/mL	113/125	90.4	(83.8 ; 94.9)	54/60	90.0	(79.5 ; 96.2)
9V	>=0.35 ug/mL	117/125	93.6	(87.8 ; 97.2)	54/60	90.0	(79.5 ; 96.2)
	>=1.0 ug/mL	101/125	80.8	(72.8 ; 87.3)	48/60	80.0	(67.7 ; 89.2)
14	>=0.35 ug/mL	124/125	99.2	(95.6 ; 100)	59/60	98.3	(91.1 ; 100)
	>=1.0 ug/mL	118/125	94.4	(88.8 ; 97.7)	58/60	96.7	(88.5 ; 99.6)
18C	>=0.35 ug/mL	117/125	93.6	(87.8 ; 97.2)	51/60	85.0	(73.4 ; 92.9)
	>=1.0 ug/mL	103/125	82.4	(74.6 ; 88.6)	47/60	78.3	(65.8 ; 87.9)
19A	>=0.35 ug/mL	120/125	96.0	(90.9 ; 98.7)	60/60	100	(94.0 ; 100)
	>=1.0 ug/mL	105/125	84.0	(76.4 ; 89.9)	51/60	85.0	(73.4 ; 92.9)
19F	>=0.35 ug/mL	122/125	97.6	(93.1 ; 99.5)	55/60	91.7	(81.6 ; 97.2)
	>=1.0 ug/mL	106/125	84.8	(77.3 ; 90.6)	50/60	83.3	(71.5 ; 91.7)
23F	>=0.35 ug/mL	117/125	93.6	(87.8 ; 97.2)	54/60	90.0	(79.5 ; 96.2)
	>=1.0 ug/mL	103/125	82.4	(74.6 ; 88.6)	48/60	80.0	(67.7 ; 89.2)

n: number of subjects experiencing the endpoint listed in the first two columns
M: number of subjects with valid serology results for the particular pneumococcal serotype
N: number of subjects in Per-Protocol Analysis Set 2
Percentages are based on M.
Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)

RotaTeq Vaccine

Table 21: Summary of fold rise rate for RotaTeq vaccine 30 days after the last vaccination in infant series in Mexico – PPAS 1

			Group 1 (N=176)			Group 2 (N=81)		
Antigen	**Timepoint**	**Criteria**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Anti-rotavirus serum IgA antibodies – U/mL	D30/D0	>=3-fold rise	165/176	93.8	(89.1 ; 96.8)	74/81	91.4	(83.0 ; 96.5)
	D30/D0	>=4-fold rise	165/176	93.8	(89.1 ; 96.8)	72/81	88.9	(80.0 ; 94.8)

n: number of subjects experiencing the endpoint listed in the first two columns
M: number of subjects with valid serology results for the particular antigen
N: number of subjects in Per-Protocol Analysis Set 1
Percentages are based on M.
Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)

Table 22: Summary of geometric means for RotaTeq vaccine 30 days after the last vaccination in infant series in Mexico – PPAS 1

Antigen	TimePoint	Group 1 (N=176) M	Geometric mean	(95% CI)	Group 2 (N=81) M	Geometric mean	(95% CI)
Anti-rotavirus serum IgA antibodies – (U/mL)	D0	176	4.24	(3.84 ; 4.67)	81	4.91	(4.00 ; 6.01)
	D30	176	621	(496 ; 776)	81	572	(402 ; 815)

M: number of subjects with valid serology results for the particular antigen and time point
N: number of subjects in Per-Protocol Analysis Set 1
Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)

Hexacima Vaccine

Table 23: Summary of response rates for Hexacima before the first vaccination and 30 days after the last vaccination in the second year of life in Mexico – PPAS 2

Component	Timepoint	Criteria	Group 1 (N=126) n/M	%	(95% CI)	Group 2 (N=60) n/M	%	(95% CI)
Diphtheria	D30	>=0.1 IU/mL	125/125	100	(97.1 ; 100)	60/60	100	(94.0 ; 100)
		>=1 IU/mL	123/125	98.4	(94.3 ; 99.8)	56/60	93.3	(83.8 ; 98.2)
Tetanus	D30	>=0.1 IU/mL	125/125	100	(97.1 ; 100)	60/60	100	(94.0 ; 100)
		>=1 IU/mL	125/125	100	(97.1 ; 100)	59/60	98.3	(91.1 ; 100)
PT	D30/D0	Vaccine response*	116/125	92.8	(86.8 ; 96.7)	57/60	95.0	(86.1 ; 99.0)
FHA	D30/D0	Vaccine response*	114/125	91.2	(84.8 ; 95.5)	50/60	83.3	(71.5 ; 91.7)
Polio 1	D30	>=8 (1/dil)	125/125	100	(97.1 ; 100)	60/60	100	(94.0 ; 100)
Polio 2	D30	>=8 (1/dil)	125/125	100	(97.1 ; 100)	60/60	100	(94.0 ; 100)
Polio 3	D30	>=8 (1/dil)	125/125	100	(97.1 ; 100)	60/60	100	(94.0 ; 100)
HBs	D30	>=10 mIU/mL	125/125	100	(97.1 ; 100)	60/60	100	(94.0 ; 100)
		>=100 mIU/mL	125/125	100	(97.1 ; 100)	60/60	100	(94.0 ; 100)
PRP	D30	>=0.15 ug/mL	125/125	100	(97.1 ; 100)	59/60	98.3	(91.1 ; 100)
		>=1.0 ug/mL	125/125	100	(97.1 ; 100)	59/60	98.3	(91.1 ; 100)

n: number of subjects experiencing the endpoint listed in the first 3 columns; M: number of subjects with valid serology results for the particular antigen and time point
N: number of subjects in Per-Protocol Analysis Set 2; Percentages are based on M.
*Pertussis vaccine seroresponse: If the pre-vaccination concentration is >= 4 x LLOQ, then the post-vaccination concentration is >= pre- vaccination concentration;
If the pre-vaccination concentration is < 4 x LLOQ, then the post-booster vaccination concentration is >= 4 x LLOQ
Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)

MMR Vaccine

Table 24: Summary of response rates for MMR vaccine 30 days after the last vaccination in the second year of life in Mexico – PPAS 2

Antigen	Timepoint	Criteria	Group 1 (N=126) n/M	%	(95% CI)	Group 2 (N=60) n/M	%	(95% CI)
Measles	D30	>=255 mIU/mL	124/125	99.2	(95.6 ; 100)	60/60	100	(94.0 ; 100)
Mumps	D30	>=10 Ab units/mL	125/125	100	(97.1 ; 100)	57/59	96.6	(88.3 ; 99.6)
Rubella	D30	>=10 IU/mL	125/125	100	(97.1 ; 100)	60/60	100	(94.0 ; 100)

n: number of subjects experiencing the endpoint listed in the first three columns
M: number of subjects with valid serology results for the particular antigen
N: number of subjects in Per-Protocol Analysis Set 2
Percentages are based on M.
Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)

Russian Federation

MMR Vaccine

Table 25: Summary of response rates for MMR vaccine 30 days after the last vaccination in the second year of life in Russia – PPAS 2

			Group 3 (N=96)			Group 4 (N=50)		
Antigen	**Timepoint**	**Criteria**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Measles	D30	>=255 mIU/mL	90/96	93.8	(86.9 ; 97.7)	44/50	88.0	(75.7 ; 95.5)
Mumps	D30	>=10 Ab units/mL	86/96	89.6	(81.7 ; 94.9)	45/50	90.0	(78.2 ; 96.7)
Rubella	D30	>=10 IU/mL	92/96	95.8	(89.7 ; 98.9)	47/50	94.0	(83.5 ; 98.7)

n: number of subjects experiencing the endpoint listed in the first three columns
M: number of subjects with valid serology results for the particular antigen
N: number of subjects in Per-Protocol Analysis Set 2
Percentages are based on M.
Group 3: MenACYW conjugate vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)
Group 4: Routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)

Pentaxim Vaccine

Table 26: Summary of response rates for Pentaxim before the first vaccination and 30 days after the last vaccination in infant series in Russia – PPAS 1

				Group 3 (N=97)			Group 4 (N=53)	
Component	**Timepoint**	**Criteria**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Diphtheria	D30	>=0.1 IU/mL	94/95	98.9	(94.3 ; 100)	49/53	92.5	(81.8 ; 97.9)
		>=1 IU/mL	76/95	80.0	(70.5 ; 87.5)	38/53	71.7	(57.7 ; 83.2)
Tetanus	D30	>=0.1 IU/mL	95/95	100	(96.2 ; 100)	52/53	98.1	(89.9 ; 100)
		>=1 IU/mL	71/95	74.7	(64.8 ; 83.1)	29/53	54.7	(40.4 ; 68.4)
PT	D30/D0	Vaccine response*	92/94	97.9	(92.5 ; 99.7)	48/53	90.6	(79.3 ; 96.9)
FHA	D30/D0	Vaccine response*	92/94	97.9	(92.5 ; 99.7)	50/53	94.3	(84.3 ; 98.8)
Polio 1	D30	>=8 (1/dil)	89/89	100	(95.9 ; 100)	47/47	100	(92.5 ; 100)
Polio 2	D30	>=8 (1/dil)	89/89	100	(95.9 ; 100)	47/47	100	(92.5 ; 100)
Polio 3	D30	>=8 (1/dil)	89/89	100	(95.9 ; 100)	47/47	100	(92.5 ; 100)
PRP	D30	>=0.15 ug/mL	85/90	94.4	(87.5 ; 98.2)	47/52	90.4	(79.0 ; 96.8)
		>=1.0 ug/mL	65/90	72.2	(61.8 ; 81.1)	30/52	57.7	(43.2 ; 71.3)

n: number of subjects experiencing the endpoint listed in the first 3 columns; M: number of subjects with valid serology results for the particular antigen and time point
N: number of subjects in Per-Protocol Analysis Set 1; Percentages are based on M.
*Pertussis vaccine seroresponse: If the pre-vaccination concentration is >= 4 x LLOQ, then the post-vaccination concentration is >= pre- vaccination concentration;
If the pre-vaccination concentration is < 4 x LLOQ, then the post-booster vaccination concentration is >= 4 x LLOQ
Group 3: MenACYW conjugate vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)
Group 4: Routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)

ENGERIX-B Vaccine

Table 27: Summary of response rates 30 days after the vaccination with ENGERIX-B at 6 months of age in Russia – PPAS 1

			Group 3 (N=97)			Group 4 (N=53)		
Component	**Timepoint**	**Criteria**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
HBs	D30	>=10 mIU/mL	85/87	97.7	(91.9 ; 99.7)	49/50	98.0	(89.4 ; 99.9)
		>=100 mIU/mL	81/87	93.1	(85.6 ; 97.4)	40/50	80.0	(66.3 ; 90.0)

n: number of subjects experiencing the endpoint listed in the first 3 columns; M: number of subjects with valid serology results for the particular antigen and time point
N: number of subjects in Per-Protocol Analysis Set 1; Percentages are based on M.
Group 3: MenACYW conjugate vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)
Group 4: Routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)

Safety results

Safety Evaluations

Immediate unsolicited systemic adverse events (AEs) were collected within 30 minutes after each vaccination. Solicited AE information was collected from D0 to D07 after each vaccination; unsolicited

AE information was collected from D0 after each vaccination to the next study visit; serious adverse event (SAE) information (including adverse events of special interest [AESIs]) was collected throughout the study.

Safety Summary

Table 28: Safety overview after any vaccine injections – Overall Safety Analysis Set for Any Dose

	Group 1 (N=201)			Group 2 (N=99)			Group 3 (N=150)			Group 4 (N=75)		
Subjects experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Within 30 minutes after any vaccine injections												
Immediate unsolicited AE	0/201	0	(0 ; 1.8)	0/99	0	(0 ; 3.7)	0/150	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
Immediate unsolicited AR	0/201	0	(0 ; 1.8)	0/99	0	(0 ; 3.7)	0/150	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
Solicited reaction within solicited period after any vaccine injections	179/200	89.5	(84.4 ; 93.4)	76/99	76.8	(67.2 ; 84.7)	64/150	42.7	(34.6 ; 51.0)	34/75	45.3	(33.8 ; 57.3)
Solicited injection site reaction	156/200	78.0	(71.6 ; 83.5)	69/99	69.7	(59.6 ; 78.5)	33/150	22.0	(15.7 ; 29.5)	12/75	16.0	(8.6 ; 26.3)
MenACYW	129/200	64.5	(57.4 ; 71.1)	NA	NA	NA	17/149	11.4	(6.8 ; 17.6)	NA	NA	NA
Menveo	NA	NA	NA	63/99	63.6	(53.4 ; 73.1)	NA	NA	NA	NA	NA	NA
Prevnar 13	134/200	67.0	(60.0 ; 73.5)	59/99	59.6	(49.3 ; 69.3)	13/150	8.7	(4.7 ; 14.4)	8/75	10.7	(4.7 ; 19.9)
Hexacima	142/200	71.0	(64.2 ; 77.2)	59/99	59.6	(49.3 ; 69.3)	NA	NA	NA	NA	NA	NA
MMR	101/191	52.9	(45.5 ; 60.1)	38/91	41.8	(31.5 ; 52.6)	6/148	4.1	(1.5 ; 8.6)	5/75	6.7	(2.2 ; 14.9)
Pentaxim	NA	NA	NA	NA	NA	NA	21/149	14.1	(8.9 ; 20.7)	8/75	10.7	(4.7 ; 19.9)
ENGERIX-B	NA	NA	NA	NA	NA	NA	9/149	6.0	(2.8 ; 11.2)	6/75	8.0	(3.0 ; 16.6)
Solicited systemic reaction	163/200	81.5	(75.4 ; 86.6)	70/99	70.7	(60.7 ; 79.4)	51/150	34.0	(26.5 ; 42.2)	29/75	38.7	(27.6 ; 50.6)
Within 30 days after any vaccine injections												
Unsolicited AE	100/201	49.8	(42.6 ; 56.9)	47/99	47.5	(37.3 ; 57.8)	15/150	10.0	(5.7 ; 16.0)	6/75	8.0	(3.0 ; 16.6)
Unsolicited AR	4/201	2.0	(0.5 ; 5.0)	2/99	2.0	(0.2 ; 7.1)	0/150	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
Unsolicited non-serious AE	99/201	49.3	(42.1 ; 56.4)	47/99	47.5	(37.3 ; 57.8)	13/150	8.7	(4.7 ; 14.4)	5/75	6.7	(2.2 ; 14.9)
Unsolicited non-serious AR	4/201	2.0	(0.5 ; 5.0)	2/99	2.0	(0.2 ; 7.1)	0/150	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
Unsolicited non-serious injection site AR	4/201	2.0	(0.5 ; 5.0)	2/99	2.0	(0.2 ; 7.1)	0/150	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
Unsolicited non-serious injection site AR related to Prevnar 13	4/201	2.0	(0.5 ; 5.0)	1/99	1.0	(0 ; 5.5)	0/150	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
Unsolicited non-serious injection site AR related to Hexacima	5/201	2.5	(0.8 ; 5.7)	7/99	7.1	(2.9 ; 14.0)	NA	NA	NA	NA	NA	NA
Unsolicited non-serious injection site AR related to MMR	0/201	0	(0 ; 1.8)	0/99	0	(0 ; 3.7)	0/150	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
Unsolicited non-serious injection site AR related to Pentaxim	NA	NA	NA	NA	NA	NA	0/150	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
Unsolicited non-serious injection site AR related to ENGERIX-B	NA	NA	NA	NA	NA	NA	0/150	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
Unsolicited non-serious systemic AE	96/201	47.8	(40.7 ; 54.9)	45/99	45.5	(35.4 ; 55.8)	13/150	8.7	(4.7 ; 14.4)	5/75	6.7	(2.2 ; 14.9)
Unsolicited non-serious systemic AR	0/201	0	(0 ; 1.8)	0/99	0	(0 ; 3.7)	0/150	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
Unsolicited non-serious systemic AR related to NIMP	1/201	0.5	(0 ; 2.7)	0/99	0	(0 ; 3.7)	0/150	0	(0 ; 2.4)	1/75	1.3	(0 ; 7.2)
AE leading to study discontinuation	0/201	0	(0 ; 1.8)	0/99	0	(0 ; 3.7)	0/150	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
SAE	2/201	1.0	(0.1 ; 3.5)	1/99	1.0	(0 ; 5.5)	2/150	1.3	(0.2 ; 4.7)	1/75	1.3	(0 ; 7.2)
Death	0/201	0	(0 ; 1.8)	0/99	0	(0 ; 3.7)	0/150	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
AESI	1/201	0.5	(0 ; 2.7)	0/99	0	(0 ; 3.7)	0/150	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
During the study												
SAE	4/201	2.0	(0.5 ; 5.0)	3/99	3.0	(0.6 ; 8.6)	4/150	2.7	(0.7 ; 6.7)	2/75	2.7	(0.3 ; 9.3)
Death	0/201	0	(0 ; 1.8)	0/99	0	(0 ; 3.7)	0/150	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
AESI	1/201	0.5	(0 ; 2.7)	1/99	1.0	(0 ; 5.5)	1/150	0.7	(0 ; 3.7)	0/75	0	(0 ; 4.8)

n: number of subjects experiencing the endpoint listed in the first column; M: number of subjects with available data for the relevant endpoint
N: number of subjects in overall safety analysis set for any dose; Percentages are based on M.
AR: Reactions related to study vaccine: MenACYW/Menveo; 'Immediate unsolicited AE' is collected only for immediate unsolicited systemic AE.
Unsolicited AE' also includes immediate and serious unsolicited AEs. 'Unsolicited non-serious AE' includes any unsolicited AE that is non-serious.
Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 3: MenACYW conjugate vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)
Group 4: Routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)

Solicited Reactions Within 7 Days After Vaccine Injection

Table 29: Summary of solicited reactions within 7 days after an- vaccine injections – Overall Safety Analysis Set for Any Dose

	Group 1 (N=201)			Group 2 (N=99)			Group 3 (N=150)			Group 4 (N=75)		
Subjects experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Solicited reaction	179/200	89.5	(84.4 ; 93.4)	76/99	76.8	(67.2 ; 84.7)	64/150	42.7	(34.6 ; 51.0)	34/75	45.3	(33.8 ; 57.3)
Grade 3 solicited reaction	40/200	20.0	(14.7 ; 26.2)	21/99	21.2	(13.6 ; 30.6)	1/150	0.7	(0 ; 3.7)	0/75	0	(0 ; 4.8)
Solicited injection site reaction	156/200	78.0	(71.6 ; 83.5)	69/99	69.7	(59.6 ; 78.5)	33/150	22.0	(15.7 ; 29.5)	12/75	16.0	(8.6 ; 26.3)
MenACYW	129/200	64.5	(57.4 ; 71.1)	NA	NA	NA	17/149	11.4	(6.8 ; 17.6)	NA	NA	NA
Menveo	NA	NA	NA	63/99	63.6	(53.4 ; 73.1)	NA	NA	NA	NA	NA	NA
Prevnar 13	134/200	67.0	(60.0 ; 73.5)	59/99	59.6	(49.3 ; 69.3)	13/150	8.7	(4.7 ; 14.4)	8/75	10.7	(4.7 ; 19.9)
Hexacima	142/200	71.0	(64.2 ; 77.2)	59/99	59.6	(49.3 ; 69.3)	NA	NA	NA	NA	NA	NA
MMR	101/191	52.9	(45.5 ; 60.1)	38/91	41.8	(31.5 ; 52.6)	6/148	4.1	(1.5 ; 8.6)	5/75	6.7	(2.2 ; 14.9)
Pentaxim	NA	NA	NA	NA	NA	NA	21/149	14.1	(8.9 ; 20.7)	8/75	10.7	(4.7 ; 19.9)
ENGERIX-B	NA	NA	NA	NA	NA	NA	9/149	6.0	(2.8 ; 11.2)	6/75	8.0	(3.0 ; 16.6)
Grade 3 injection site reaction	24/200	12.0	(7.8 ; 17.3)	14/99	14.1	(8.0 ; 22.6)	0/150	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
MenACYW	12/200	6.0	(3.1 ; 10.2)	NA	NA	NA	0/149	0	(0 ; 2.4)	NA	NA	NA
Menveo	NA	NA	NA	10/99	10.1	(5.0 ; 17.8)	NA	NA	NA	NA	NA	NA
Prevnar 13	15/200	7.5	(4.3 ; 12.1)	9/99	9.1	(4.2 ; 16.6)	0/150	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
Hexacima	16/200	8.0	(4.6 ; 12.7)	9/99	9.1	(4.2 ; 16.6)	NA	NA	NA	NA	NA	NA
MMR	5/191	2.6	(0.9 ; 6.0)	4/91	4.4	(1.2 ; 10.9)	0/148	0	(0 ; 2.5)	0/75	0	(0 ; 4.8)
Pentaxim	NA	NA	NA	NA	NA	NA	0/149	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
ENGERIX-B	NA	NA	NA	NA	NA	NA	0/149	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
Solicited systemic reaction	163/200	81.5	(75.4 ; 86.6)	70/99	70.7	(60.7 ; 79.4)	51/150	34.0	(26.5 ; 42.2)	29/75	38.7	(27.6 ; 50.6)
Grade 3 systemic reaction	23/200	11.5	(7.4 ; 16.8)	12/99	12.1	(6.4 ; 20.2)	1/150	0.7	(0 ; 3.7)	0/75	0	(0 ; 4.8)

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

Solicited Injection Site Reactions

Table 30: Solicited injection site reactions after any vaccine injections, by maximum intensity during the solicited period – Overall Safety Analysis Set for Any Dose

		Group 1 (N=201)			Group 2 (N=99)			Group 3 (N=150)			Group 4 (N=75)		
Subjects experiencing at least one:	**Maximum intensity**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
MenACYW													
Injection Site Tenderness	Any	121/200	60.5	(53.4 ; 67.3)	NA	NA	NA	9/149	6.0	(2.8 ; 11.2)	NA	NA	NA
	Grade 1	86/200	43.0	(36.0 ; 50.2)	NA	NA	NA	6/149	4.0	(1.5 ; 8.6)	NA	NA	NA
	Grade 2	25/200	12.5	(8.3 ; 17.9)	NA	NA	NA	3/149	2.0	(0.4 ; 5.8)	NA	NA	NA
	Grade 3	10/200	5.0	(2.4 ; 9.0)	NA	NA	NA	0/149	0	(0 ; 2.4)	NA	NA	NA
Injection Site Erythema	Any	52/200	26.0	(20.1 ; 32.7)	NA	NA	NA	11/149	7.4	(3.7 ; 12.8)	NA	NA	NA
	Grade 1	46/200	23.0	(17.4 ; 29.5)	NA	NA	NA	11/149	7.4	(3.7 ; 12.8)	NA	NA	NA
	Grade 2	4/200	2.0	(0.5 ; 5.0)	NA	NA	NA	0/149	0	(0 ; 2.4)	NA	NA	NA
	Grade 3	2/200	1.0	(0.1 ; 3.6)	NA	NA	NA	0/149	0	(0 ; 2.4)	NA	NA	NA
Injection Site Swelling	Any	24/200	12.0	(7.8 ; 17.3)	NA	NA	NA	6/149	4.0	(1.5 ; 8.6)	NA	NA	NA
	Grade 1	24/200	12.0	(7.8 ; 17.3)	NA	NA	NA	6/149	4.0	(1.5 ; 8.6)	NA	NA	NA
	Grade 2	0/200	0	(0 ; 1.8)	NA	NA	NA	0/149	0	(0 ; 2.4)	NA	NA	NA
	Grade 3	0/200	0	(0 ; 1.8)	NA	NA	NA	0/149	0	(0 ; 2.4)	NA	NA	NA
Menveo													
Injection Site Tenderness	Any	NA	NA	NA	60/99	60.6	(50.3 ; 70.3)	NA	NA	NA	NA	NA	NA
	Grade 1	NA	NA	NA	36/99	36.4	(26.9 ; 46.6)	NA	NA	NA	NA	NA	NA
	Grade 2	NA	NA	NA	15/99	15.2	(8.7 ; 23.8)	NA	NA	NA	NA	NA	NA
	Grade 3	NA	NA	NA	9/99	9.1	(4.2 ; 16.6)	NA	NA	NA	NA	NA	NA

Injection Site Erythema	Any	NA	NA	NA	13/99	13.1	(7.2 ; 21.4)	NA	NA	NA	NA	NA	NA
	Grade 1	NA	NA	NA	10/99	10.1	(5.0 ; 17.8)	NA	NA	NA	NA	NA	NA
	Grade 2	NA	NA	NA	2/99	2.0	(0.2 ; 7.1)	NA	NA	NA	NA	NA	NA
	Grade 3	NA	NA	NA	1/99	1.0	(0 ; 5.5)	NA	NA	NA	NA	NA	NA
Injection Site Swelling	Any	NA	NA	NA	9/99	9.1	(4.2 ; 16.6)	NA	NA	NA	NA	NA	NA
	Grade 1	NA	NA	NA	7/99	7.1	(2.9 ; 14.0)	NA	NA	NA	NA	NA	NA
	Grade 2	NA	NA	NA	2/99	2.0	(0.2 ; 7.1)	NA	NA	NA	NA	NA	NA
	Grade 3	NA	NA	NA	0/99	0	(0 ; 3.7)	NA	NA	NA	NA	NA	NA
Prevnar 13													
Injection Site Tenderness	Any	125/200	62.5	(55.4 ; 69.2)	57/99	57.6	(47.2 ; 67.5)	8/150	5.3	(2.3 ; 10.2)	7/75	9.3	(3.8 ; 18.3)
	Grade 1	78/200	39.0	(32.2 ; 46.1)	36/99	36.4	(26.9 ; 46.6)	6/150	4.0	(1.5 ; 8.5)	7/75	9.3	(3.8 ; 18.3)
	Grade 2	32/200	16.0	(11.2 ; 21.8)	12/99	12.1	(6.4 ; 20.2)	2/150	1.3	(0.2 ; 4.7)	0/75	0	(0 ; 4.8)
	Grade 3	15/200	7.5	(4.3 ; 12.1)	9/99	9.1	(4.2 ; 16.6)	0/150	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
Injection Site Erythema	Any	48/200	24.0	(18.3 ; 30.5)	20/99	20.2	(12.8 ; 29.5)	9/150	6.0	(2.8 ; 11.1)	4/75	5.3	(1.5 ; 13.1)
	Grade 1	47/200	23.5	(17.8 ; 30.0)	16/99	16.2	(9.5 ; 24.9)	9/150	6.0	(2.8 ; 11.1)	4/75	5.3	(1.5 ; 13.1)
	Grade 2	1/200	0.5	(0 ; 2.8)	4/99	4.0	(1.1 ; 10.0)	0/150	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
	Grade 3	0/200	0	(0 ; 1.8)	0/99	0	(0 ; 3.7)	0/150	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
Injection Site Swelling	Any	21/200	10.5	(6.6 ; 15.6)	4/99	4.0	(1.1 ; 10.0)	5/150	3.3	(1.1 ; 7.6)	4/75	5.3	(1.5 ; 13.1)
	Grade 1	20/200	10.0	(6.2 ; 15.0)	2/99	2.0	(0.2 ; 7.1)	5/150	3.3	(1.1 ; 7.6)	4/75	5.3	(1.5 ; 13.1)
	Grade 2	1/200	0.5	(0 ; 2.8)	2/99	2.0	(0.2 ; 7.1)	0/150	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
	Grade 3	0/200	0	(0 ; 1.8)	0/99	0	(0 ; 3.7)	0/150	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
Hexacima													
Injection Site Tenderness	Any	132/200	66.0	(59.0 ; 72.5)	56/99	56.6	(46.2 ; 66.5)	NA	NA	NA	NA	NA	NA
	Grade 1	81/200	40.5	(33.6 ; 47.7)	33/99	33.3	(24.2 ; 43.5)	NA	NA	NA	NA	NA	NA
	Grade 2	38/200	19.0	(13.8 ; 25.1)	15/99	15.2	(8.7 ; 23.8)	NA	NA	NA	NA	NA	NA
	Grade 3	13/200	6.5	(3.5 ; 10.9)	8/99	8.1	(3.6 ; 15.3)	NA	NA	NA	NA	NA	NA
Injection Site Erythema	Any	73/200	36.5	(29.8 ; 43.6)	20/99	20.2	(12.8 ; 29.5)	NA	NA	NA	NA	NA	NA
	Grade 1	56/200	28.0	(21.9 ; 34.8)	11/99	11.1	(5.7 ; 19.0)	NA	NA	NA	NA	NA	NA
	Grade 2	14/200	7.0	(3.9 ; 11.5)	8/99	8.1	(3.6 ; 15.3)	NA	NA	NA	NA	NA	NA
	Grade 3	3/200	1.5	(0.3 ; 4.3)	1/99	1.0	(0 ; 5.5)	NA	NA	NA	NA	NA	NA
Injection Site Swelling	Any	32/200	16.0	(11.2 ; 21.8)	7/99	7.1	(2.9 ; 14.0)	NA	NA	NA	NA	NA	NA
	Grade 1	30/200	15.0	(10.4 ; 20.7)	6/99	6.1	(2.3 ; 12.7)	NA	NA	NA	NA	NA	NA
	Grade 2	2/200	1.0	(0.1 ; 3.6)	1/99	1.0	(0 ; 5.5)	NA	NA	NA	NA	NA	NA
	Grade 3	0/200	0	(0 ; 1.8)	0/99	0	(0 ; 3.7)	NA	NA	NA	NA	NA	NA
MMR													
Injection Site Tenderness	Any	69/191	36.1	(29.3 ; 43.4)	24/91	26.4	(17.7 ; 36.7)	3/148	2.0	(0.4 ; 5.8)	3/75	4.0	(0.8 ; 11.2)
	Grade 1	52/191	27.2	(21.0 ; 34.1)	16/91	17.6	(10.4 ; 27.0)	2/148	1.4	(0.2 ; 4.8)	3/75	4.0	(0.8 ; 11.2)
	Grade 2	14/191	7.3	(4.1 ; 12.0)	7/91	7.7	(3.1 ; 15.2)	1/148	0.7	(0 ; 3.7)	0/75	0	(0 ; 4.8)
	Grade 3	3/191	1.6	(0.3 ; 4.5)	1/91	1.1	(0 ; 6.0)	0/148	0	(0 ; 2.5)	0/75	0	(0 ; 4.8)
Injection Site Erythema	Any	66/191	34.6	(27.8 ; 41.8)	27/91	29.7	(20.5 ; 40.2)	5/148	3.4	(1.1 ; 7.7)	3/75	4.0	(0.8 ; 11.2)
	Grade 1	20/191	10.5	(6.5 ; 15.7)	4/91	4.4	(1.2 ; 10.9)	5/148	3.4	(1.1 ; 7.7)	3/75	4.0	(0.8 ; 11.2)
	Grade 2	43/191	22.5	(16.8 ; 29.1)	19/91	20.9	(13.1 ; 30.7)	0/148	0	(0 ; 2.5)	0/75	0	(0 ; 4.8)
	Grade 3	3/191	1.6	(0.3 ; 4.5)	4/91	4.4	(1.2 ; 10.9)	0/148	0	(0 ; 2.5)	0/75	0	(0 ; 4.8)
Injection Site Swelling	Any	14/191	7.3	(4.1 ; 12.0)	6/91	6.6	(2.5 ; 13.8)	1/148	0.7	(0 ; 3.7)	1/75	1.3	(0 ; 7.2)
	Grade 1	11/191	5.8	(2.9 ; 10.1)	3/91	3.3	(0.7 ; 9.3)	1/148	0.7	(0 ; 3.7)	1/75	1.3	(0 ; 7.2)
	Grade 2	3/191	1.6	(0.3 ; 4.5)	3/91	3.3	(0.7 ; 9.3)	0/148	0	(0 ; 2.5)	0/75	0	(0 ; 4.8)
	Grade 3	0/191	0	(0 ; 1.9)	0/91	0	(0 ; 4.0)	0/148	0	(0 ; 2.5)	0/75	0	(0 ; 4.8)
Pentaxim													
Injection Site Tenderness	Any	NA	NA	NA	NA	NA	NA	7/149	4.7	(1.9 ; 9.4)	6/75	8.0	(3.0 ; 16.6)
	Grade 1	NA	NA	NA	NA	NA	NA	7/149	4.7	(1.9 ; 9.4)	5/75	6.7	(2.2 ; 14.9)
	Grade 2	NA	NA	NA	NA	NA	NA	0/149	0	(0 ; 2.4)	1/75	1.3	(0 ; 7.2)
	Grade 3	NA	NA	NA	NA	NA	NA	0/149	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
Injection Site Erythema	Any	NA	NA	NA	NA	NA	NA	18/149	12.1	(7.3 ; 18.4)	4/75	5.3	(1.5 ; 13.1)
	Grade 1	NA	NA	NA	NA	NA	NA	18/149	12.1	(7.3 ; 18.4)	4/75	5.3	(1.5 ; 13.1)
	Grade 2	NA	NA	NA	NA	NA	NA	0/149	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
	Grade 3	NA	NA	NA	NA	NA	NA	0/149	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
Injection Site Swelling	Any	NA	NA	NA	NA	NA	NA	11/149	7.4	(3.7 ; 12.8)	3/75	4.0	(0.8 ; 11.2)
	Grade 1	NA	NA	NA	NA	NA	NA	11/149	7.4	(3.7 ; 12.8)	3/75	4.0	(0.8 ; 11.2)
	Grade 2	NA	NA	NA	NA	NA	NA	0/149	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
	Grade 3	NA	NA	NA	NA	NA	NA	0/149	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
ENGERIX-B													
Injection Site Tenderness	Any	NA	NA	NA	NA	NA	NA	5/149	3.4	(1.1 ; 7.7)	3/75	4.0	(0.8 ; 11.2)
	Grade 1	NA	NA	NA	NA	NA	NA	5/149	3.4	(1.1 ; 7.7)	3/75	4.0	(0.8 ; 11.2)
	Grade 2	NA	NA	NA	NA	NA	NA	0/149	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
	Grade 3	NA	NA	NA	NA	NA	NA	0/149	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)

Injection Site Erythema	Any	NA	NA	NA	NA	NA	NA	8/149	5.4	(2.3 ; 10.3)	4/75	5.3	(1.5 ; 13.1)
	Grade 1	NA	NA	NA	NA	NA	NA	8/149	5.4	(2.3 ; 10.3)	4/75	5.3	(1.5 ; 13.1)
	Grade 2	NA	NA	NA	NA	NA	NA	0/149	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
	Grade 3	NA	NA	NA	NA	NA	NA	0/149	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
Injection Site Swelling	Any	NA	NA	NA	NA	NA	NA	5/149	3.4	(1.1 ; 7.7)	1/75	1.3	(0 ; 7.2)
	Grade 1	NA	NA	NA	NA	NA	NA	5/149	3.4	(1.1 ; 7.7)	1/75	1.3	(0 ; 7.2)
	Grade 2	NA	NA	NA	NA	NA	NA	0/149	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
	Grade 3	NA	NA	NA	NA	NA	NA	0/149	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)

n: number of subjects experiencing the endpoint listed in the first 2 columns
M: number of subjects with available data for the relevant endpoint
N: number of subjects in overall safety analysis set for any dose
Percentages are based on M.
Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 3: MenACYW conjugate vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)
Group 4: Routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)

Solicited Systemic Reactions

Table 31: Solicited systemic reactions after any vaccine injections, by maximum intensity during the solicited period – Overall Safety Analysis Set for Any Dose

		Group 1 (N=201)			Group 2 (N=99)			Group 3 (N=150)			Group 4 (N=75)		
Subjects experiencing at least one:	**Maximum intensity**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Fever	Any	84/199	42.2	(35.3 ; 49.4)	33/98	33.7	(24.4 ; 43.9)	11/149	7.4	(3.7 ; 12.8)	6/75	8.0	(3.0 ; 16.6)
	Grade 1	57/199	28.6	(22.5 ; 35.5)	25/98	25.5	(17.2 ; 35.3)	10/149	6.7	(3.3 ; 12.0)	5/75	6.7	(2.2 ; 14.9)
	Grade 2	23/199	11.6	(7.5 ; 16.8)	8/98	8.2	(3.6 ; 15.5)	1/149	0.7	(0 ; 3.7)	1/75	1.3	(0 ; 7.2)
	Grade 3	4/199	2.0	(0.6 ; 5.1)	0/98	0	(0 ; 3.7)	0/149	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
Vomiting	Any	39/200	19.5	(14.2 ; 25.7)	11/99	11.1	(5.7 ; 19.0)	6/150	4.0	(1.5 ; 8.5)	0/75	0	(0 ; 4.8)
	Grade 1	29/200	14.5	(9.9 ; 20.2)	7/99	7.1	(2.9 ; 14.0)	3/150	2.0	(0.4 ; 5.7)	0/75	0	(0 ; 4.8)
	Grade 2	10/200	5.0	(2.4 ; 9.0)	4/99	4.0	(1.1 ; 10.0)	3/150	2.0	(0.4 ; 5.7)	0/75	0	(0 ; 4.8)
	Grade 3	0/200	0	(0 ; 1.8)	0/99	0	(0 ; 3.7)	0/150	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
Crying abnormal	Any	117/200	58.5	(51.3 ; 65.4)	50/99	50.5	(40.3 ; 60.7)	18/150	12.0	(7.3 ; 18.3)	6/75	8.0	(3.0 ; 16.6)
	Grade 1	81/200	40.5	(33.6 ; 47.7)	32/99	32.3	(23.3 ; 42.5)	15/150	10.0	(5.7 ; 16.0)	5/75	6.7	(2.2 ; 14.9)
	Grade 2	28/200	14.0	(9.5 ; 19.6)	14/99	14.1	(8.0 ; 22.6)	3/150	2.0	(0.4 ; 5.7)	1/75	1.3	(0 ; 7.2)
	Grade 3	8/200	4.0	(1.7 ; 7.7)	4/99	4.0	(1.1 ; 10.0)	0/150	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
Drowsiness	Any	80/200	40.0	(33.2 ; 47.1)	36/99	36.4	(26.9 ; 46.6)	33/150	22.0	(15.7 ; 29.5)	17/75	22.7	(13.8 ; 33.8)
	Grade 1	58/200	29.0	(22.8 ; 35.8)	24/99	24.2	(16.2 ; 33.9)	25/150	16.7	(11.1 ; 23.6)	14/75	18.7	(10.6 ; 29.3)
	Grade 2	15/200	7.5	(4.3 ; 12.1)	8/99	8.1	(3.6 ; 15.3)	7/150	4.7	(1.9 ; 9.4)	3/75	4.0	(0.8 ; 11.2)
	Grade 3	7/200	3.5	(1.4 ; 7.1)	4/99	4.0	(1.1 ; 10.0)	1/150	0.7	(0 ; 3.7)	0/75	0	(0 ; 4.8)
Appetite lost	Any	72/200	36.0	(29.4 ; 43.1)	33/99	33.3	(24.2 ; 43.5)	26/150	17.3	(11.6 ; 24.4)	11/75	14.7	(7.6 ; 24.7)
	Grade 1	57/200	28.5	(22.4 ; 35.3)	26/99	26.3	(17.9 ; 36.1)	17/150	11.3	(6.7 ; 17.5)	9/75	12.0	(5.6 ; 21.6)
	Grade 2	12/200	6.0	(3.1 ; 10.2)	7/99	7.1	(2.9 ; 14.0)	9/150	6.0	(2.8 ; 11.1)	2/75	2.7	(0.3 ; 9.3)
	Grade 3	3/200	1.5	(0.3 ; 4.3)	0/99	0	(0 ; 3.7)	0/150	0	(0 ; 2.4)	0/75	0	(0 ; 4.8)
Irritability	Any	134/200	67.0	(60.0 ; 73.5)	58/99	58.6	(48.2 ; 68.4)	32/150	21.3	(15.1 ; 28.8)	20/75	26.7	(17.1 ; 38.1)
	Grade 1	71/200	35.5	(28.9 ; 42.6)	29/99	29.3	(20.6 ; 39.3)	21/150	14.0	(8.9 ; 20.6)	16/75	21.3	(12.7 ; 32.3)
	Grade 2	54/200	27.0	(21.0 ; 33.7)	22/99	22.2	(14.5 ; 31.7)	10/150	6.7	(3.2 ; 11.9)	4/75	5.3	(1.5 ; 13.1)
	Grade 3	9/200	4.5	(2.1 ; 8.4)	7/99	7.1	(2.9 ; 14.0)	1/150	0.7	(0 ; 3.7)	0/75	0	(0 ; 4.8)

n: number of subjects experiencing the endpoint listed in the first 2 columns
M: number of subjects with available data for the relevant endpoint
N: number of subjects in overall safety analysis set for any dose
Percentages are based on M.
Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 3: MenACYW conjugate vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)
Group 4: Routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)

Unsolicited Non-Serious Adverse Events Between D0 and D30

There were no immediate unsolicited non-serious AEs or ARs reported within 30 minutes after any vaccination in any of the groups.

Table 32: Summary of unsolicited AEs within 30 days after any vaccine injections - Overall Safety Analysis Set for Any Dose

	Group 1 (N=201)				Group 2 (N=99)				Group 3 (N=150)				Group 4 (N=75)			
Subjects experiencing at least one:	**n**	**%**	**(95% CI)**	**n AEs**	**n**	**%**	**(95% CI)**	**n AEs**	**n**	**%**	**(95% CI)**	**n AEs**	**n**	**%**	**(95% CI)**	**n AEs**
Immediate unsolicited AE	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
Grade 3 immediate unsolicited AE	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
Immediate unsolicited AR	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
Grade 3 immediate unsolicited AR	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
Unsolicited AE	100	49.8	(42.6 ; 56.9)	184	47	47.5	(37.3 ; 57.8)	94	15	10.0	(5.7 ; 16.0)	24	6	8.0	(3.0 ; 16.6)	13
Grade 3 unsolicited AE	6	3.0	(1.1 ; 6.4)	8	0	0	(0 ; 3.7)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
Unsolicited AR	4	2.0	(0.5 ; 5.0)	4	2	2.0	(0.2 ; 7.1)	2	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
Grade 3 unsolicited AR	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
Unsolicited injection site AR	4	2.0	(0.5 ; 5.0)	4	2	2.0	(0.2 ; 7.1)	2	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
Grade 3 unsolicited injection site AR	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
Unsolicited injection site AR related to Prevnar 13	4	2.0	(0.5 ; 5.0)	4	1	1.0	(0 ; 5.5)	1	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
Grade 3 unsolicited injection site AR related to Prevnar 13	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
Unsolicited injection site AR related to Hexacima	5	2.5	(0.8 ; 5.7)	6	7	7.1	(2.9 ; 14.0)	9	NA	NA	NA	NA	NA	NA	NA	NA
Grade 3 unsolicited injection site AR related to Hexacima	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	NA	NA	NA	NA	NA	NA	NA	NA
Unsolicited injection site AR related to MMR	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
Grade 3 unsolicited injection site AR related to MMR	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
Unsolicited injection site AR related to Pentaxim	NA	NA	NA	NA	NA	NA	NA	NA	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
Grade 3 unsolicited injection site AR related to Pentaxim	NA	NA	NA	NA	NA	NA	NA	NA	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
Unsolicited injection site AR related to ENGERIX-B	NA	NA	NA	NA	NA	NA	NA	NA	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
Grade 3 unsolicited injection site AR related to ENGERIX-B	NA	NA	NA	NA	NA	NA	NA	NA	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
Unsolicited systemic AE	97	48.3	(41.2 ; 55.4)	170	45	45.5	(35.4 ; 55.8)	82	15	10.0	(5.7 ; 16.0)	24	6	8.0	(3.0 ; 16.6)	13
Grade 3 unsolicited systemic AE	6	3.0	(1.1 ; 6.4)	8	0	0	(0 ; 3.7)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
Unsolicited systemic AR	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
Grade 3 unsolicited systemic AR	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
Unsolicited systemic AR related to NIMP	1	0.5	(0 ; 2.7)	1	0	0	(0 ; 3.7)	0	0	0	(0 ; 2.4)	0	1	1.3	(0 ; 7.2)	2
Grade 3 unsolicited systemic AR related to NIMP	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
SAE	2	1.0	(0.1 ; 3.5)	2	1	1.0	(0 ; 5.5)	1	2	1.3	(0.2 ; 4.7)	2	1	1.3	(0 ; 7.2)	1
Grade 3 SAE	2	1.0	(0.1 ; 3.5)	2	0	0	(0 ; 3.7)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0

n: number of subjects experiencing the endpoint listed in the first column; n AEs: number of AEs
N: number of subjects in overall safety analysis set for any dose; Percentages are based on N.
AR: reactions related to study vaccine: MenACYW/Menveo; 'Immediate unsolicited AE' is collected only for immediate unsolicited systemic AE.
"Unsolicited AE" also includes immediate and serious unsolicited AEs.
Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 3: MenACYW conjugate vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)
Group 4: Routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)

Unsolicited Non-Serious Adverse Reactions Between D0 and D30

Table 33: Unsolicited ARs within 30 days after any vaccine injections, by maximum intensity, time of onset and duration - Overall Safety Analysis Set for Any Dose

	Group 1 (N=201)				Group 2 (N=99)				Group 3 (N=150)				Group 4 (N=75)			
Subjects experiencing at least one:	**n**	**%**	**(95% CI)**	**n ARs**	**n**	**%**	**(95% CI)**	**n ARs**	**n**	**%**	**(95% CI)**	**n ARs**	**n**	**%**	**(95% CI)**	**n ARs**
Unsolicited AR	4	2.0	(0.5 ; 5.0)	4	2	2.0	(0.2 ; 7.1)	2	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
Maximum intensity																
Missing	2	1.0	(0.1 ; 3.5)	2	0	0	(0 ; 3.7)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
Grade 1	1	0.5	(0 ; 2.7)	1	2	2.0	(0.2 ; 7.1)	2	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
Grade 2	1	0.5	(0 ; 2.7)	1	0	0	(0 ; 3.7)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
Grade 3	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
Time of onset																
Missing	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
D0-D3	3	1.5	(0.3 ; 4.3)	3	2	2.0	(0.2 ; 7.1)	2	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
D4-D7	1	0.5	(0 ; 2.7)	1	0	0	(0 ; 3.7)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
D8-D14	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
>=D15	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
Duration																
Missing	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
1-3 days	2	1.0	(0.1 ; 3.5)	2	1	1.0	(0 ; 5.5)	1	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
4-7 days	1	0.5	(0 ; 2.7)	1	1	1.0	(0 ; 5.5)	1	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
8 days or more	1	0.5	(0 ; 2.7)	1	0	0	(0 ; 3.7)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0

n: number of subjects experiencing the endpoint listed in the first column; n ARs: number of ARs
N: number of subjects in overall safety analysis set for any dose
Percentages are based on N.
AR: reactions related to study vaccine: MenACYW/Menveo
Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 3: MenACYW conjugate vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)
Group 4: Routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)

Table 34: Unsolicited ARs within 30 days after any vaccine injections, by system organ class and preferred term - Overall Safety Analysis Set for Any Dose

	Group 1 (N=201)				Group 2 (N=99)				Group 3 (N=150)				Group 4 (N=75)			
Subjects experiencing at least one:	**n**	**%**	**(95% CI)**	**n ARs**	**n**	**%**	**(95% CI)**	**n ARs**	**n**	**%**	**(95% CI)**	**n ARs**	**n**	**%**	**(95% CI)**	**n ARs**
Unsolicited AR	4	2.0	(0.5 ; 5.0)	4	2	2.0	(0.2 ; 7.1)	2	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
General disorders and administration site conditions	4	2.0	(0.5 ; 5.0)	4	2	2.0	(0.2 ; 7.1)	2	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
Injection site haemorrhage	2	1.0	(0.1 ; 3.5)	2	0	0	(0 ; 3.7)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
Injection site haematoma	1	0.5	(0 ; 2.7)	1	1	1.0	(0 ; 5.5)	1	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0
Injection site rash	1	0.5	(0 ; 2.7)	1	1	1.0	(0 ; 5.5)	1	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0

n: number of subjects experiencing the endpoint listed in the first column.
n ARs: number of ARs
N: number of subjects in overall safety analysis set for any dose
Percentages are based on N. AR: reactions related to study vaccine: MenACYW/Menveo
Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 3: MenACYW conjugate vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)
Group 4: Routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)

Deaths and SAEs

There were no deaths reported in the study.

An overview of SAEs in the overall safety analysis set for any dose is presented in the Table below.

Table 35: Overview of SAEs - Overall Safety Analysis Set for Any Dose

	Group 1 (N=201)								Group 2 (N=99)							
	All SAEs				Related SAEs				All SAEs				Related SAEs			
Subjects experiencing at least one SAE:	**n**	**%**	**(95% CI)**	**n SAEs**	**n**	**%**	**(95% CI)**	**n SAEs**	**n**	**%**	**(95% CI)**	**n SAEs**	**n**	**%**	**(95% CI)**	**n SAEs**
Within 7 days after any vaccine injections	0	0	(0 ; 1.8)	0	0	0	(0 ; 1.8)	0	1	1.0	(0 ; 5.5)	1	0	0	(0 ; 3.7)	0
Within 7 days after vaccine injections at 2 months of age	0	0	(0 ; 1.8)	0	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 3.7)	0
Within 7 days after vaccine injections at 3 months of age	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Within 7 days after vaccine injections at 4 months of age	0	0	(0 ; 1.8)	0	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 3.7)	0
Within 7 days after vaccine injections at 4.5 months of age	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Within 7 days after vaccine injections at 6 months of age	0	0	(0 ; 1.8)	0	0	0	(0 ; 1.8)	0	1	1.0	(0 ; 5.5)	1	0	0	(0 ; 3.7)	0
Within 7 days after vaccine injections at 12 months of age	0	0	(0 ; 1.8)	0	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 3.7)	0
Within 30 days after any vaccine injections	2	1.0	(0.1 ; 3.5)	2	0	0	(0 ; 1.8)	0	1	1.0	(0 ; 5.5)	1	0	0	(0 ; 3.7)	0
Within 30 days after vaccine injections at 2 months of age	0	0	(0 ; 1.8)	0	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 3.7)	0
Within 30 days after vaccine injections at 3 months of age	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Within 30 days after vaccine injections at 4 months of age	1	0.5	(0 ; 2.7)	1	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 3.7)	0
Within 30 days after vaccine injections at 4.5 months of age	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Within 30 days after vaccine injections at 6 months of age	0	0	(0 ; 1.8)	0	0	0	(0 ; 1.8)	0	1	1.0	(0 ; 5.5)	1	0	0	(0 ; 3.7)	0
Within 30 days after vaccine injections at 12 months of age	1	0.5	(0 ; 2.7)	1	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 3.7)	0
During the study	4	2.0	(0.5 ; 5.0)	4	0	0	(0 ; 1.8)	0	3	3.0	(0.6 ; 8.6)	3	0	0	(0 ; 3.7)	0

	Group 3 (N=150)								Group 4 (N=75)							
	All SAEs				Related SAEs				All SAEs				Related SAEs			
Subjects experiencing at least one SAE:	**n**	**%**	**(95% CI)**	**n SAEs**	**n**	**%**	**(95% CI)**	**n SAEs**	**n**	**%**	**(95% CI)**	**n SAEs**	**n**	**%**	**(95% CI)**	**n SAEs**
Within 7 days after any vaccine injections	0	0	(0 ; 2.4)	0	0	0	(0 ; 2.4)	0	1	1.3	(0 ; 7.2)	1	0	0	(0 ; 4.8)	0
Within 7 days after vaccine injections at 2 months of age	0	0	(0 ; 2.4)	0	0	0	(0 ; 2.4)	0	1	1.3	(0 ; 7.2)	1	0	0	(0 ; 4.8)	0
Within 7 days after vaccine injections at 3 months of age	0	0	(0 ; 2.4)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0	0	0	(0 ; 4.8)	0
Within 7 days after vaccine injections at 4 months of age	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Within 7 days after vaccine injections at 4.5 months of age	0	0	(0 ; 2.4)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0	0	0	(0 ; 4.8)	0
Within 7 days after vaccine injections at 6 months of age	0	0	(0 ; 2.4)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0	0	0	(0 ; 4.8)	0
Within 7 days after vaccine injections at 12 months of age	0	0	(0 ; 2.4)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0	0	0	(0 ; 4.8)	0
Within 30 days after any vaccine injections	2	1.3	(0.2 ; 4.7)	2	0	0	(0 ; 2.4)	0	1	1.3	(0 ; 7.2)	1	0	0	(0 ; 4.8)	0
Within 30 days after vaccine injections at 2 months of age	1	0.7	(0 ; 3.7)	1	0	0	(0 ; 2.4)	0	1	1.3	(0 ; 7.2)	1	0	0	(0 ; 4.8)	0
Within 30 days after vaccine injections at 3 months of age	0	0	(0 ; 2.4)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0	0	0	(0 ; 4.8)	0
Within 30 days after vaccine injections at 4 months of age	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Within 30 days after vaccine injections at 4.5 months of age	1	0.7	(0 ; 3.7)	1	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0	0	0	(0 ; 4.8)	0
Within 30 days after vaccine injections at 6 months of age	0	0	(0 ; 2.4)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0	0	0	(0 ; 4.8)	0
Within 30 days after vaccine injections at 12 months of age	0	0	(0 ; 2.4)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0	0	0	(0 ; 4.8)	0
During the study	4	2.7	(0.7 ; 6.7)	5	0	0	(0 ; 2.4)	0	2	2.7	(0.3 ; 9.3)	3	0	0	(0 ; 4.8)	0

n: number of subjects experiencing the endpoint listed in the first column
n SAEs: number of SAEs
N: number of subjects in overall safety analysis set for any dose; Percentages are based on N.
Related SAEs: relationship reported by an investigator as related to study vaccine: MenACYW/Menveo. If the relationship is missing, the SAE will be considered as related
Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age (Mexico)
Group 3: MenACYW conjugate vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)
Group 4: Routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age (The Russian Federation)

Discontinuations due to Adverse Events

No subjects were discontinued from the study due to an AE.

Adverse Events of Special Interest

Table 36: Overview of AESI - Overall Safety Analysis Set for Any Dose

	Group 1 (N=201)								Group 2 (N=99)							
	All AESIs				Related AESIs				All AESIs				Related AESIs			
Subjects experiencing at least one AESI:	**n**	**%**	**(95% CI)**	**n AESIs**	**n**	**%**	**(95% CI)**	**n AESIs**	**n**	**%**	**(95% CI)**	**n AESIs**	**n**	**%**	**(95% CI)**	**n AESIs**
Within 7 days after any vaccine injections	0	0	(0 ; 1.8)	0	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 3.7)	0
Within 7 days after vaccine injections at 2 months of age	0	0	(0 ; 1.8)	0	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 3.7)	0
Within 7 days after vaccine injections at 3 months of age	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Within 7 days after vaccine injections at 4 months of age	0	0	(0 ; 1.8)	0	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 3.7)	0
Within 7 days after vaccine injections at 4.5 months of age	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Within 7 days after vaccine injections at 6 months of age	0	0	(0 ; 1.8)	0	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 3.7)	0
Within 7 days after vaccine injections at 12 months of age	0	0	(0 ; 1.8)	0	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 3.7)	0
Within 30 days after any vaccine injections	1	0.5	(0 ; 2.7)	1	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 3.7)	0
Within 30 days after vaccine injections at 2 months of age	0	0	(0 ; 1.8)	0	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 3.7)	0
Within 30 days after vaccine injections at 3 months of age	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Within 30 days after vaccine injections at 4 months of age	1	0.5	(0 ; 2.7)	1	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 3.7)	0
Within 30 days after vaccine injections at 4.5 months of age	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Within 30 days after vaccine injections at 6 months of age	0	0	(0 ; 1.8)	0	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 3.7)	0
Within 30 days after vaccine injections at 12 months of age	0	0	(0 ; 1.8)	0	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 3.7)	0
During the study	1	0.5	(0 ; 2.7)	1	0	0	(0 ; 1.8)	0	1	1.0	(0 ; 5.5)	1	0	0	(0 ; 3.7)	0
Within 7 days after any vaccine injections	0	0	(0 ; 2.4)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0	0	0	(0 ; 4.8)	0
Within 7 days after vaccine injections at 2 months of age	0	0	(0 ; 2.4)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0	0	0	(0 ; 4.8)	0
Within 7 days after vaccine injections at 3 months of age	0	0	(0 ; 2.4)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0	0	0	(0 ; 4.8)	0
Within 7 days after vaccine injections at 4 months of age	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Within 7 days after vaccine injections at 4.5 months of age	0	0	(0 ; 2.4)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0	0	0	(0 ; 4.8)	0
Within 7 days after vaccine injections at 6 months of age	0	0	(0 ; 2.4)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0	0	0	(0 ; 4.8)	0
Within 7 days after vaccine injections at 12 months of age	0	0	(0 ; 2.4)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0	0	0	(0 ; 4.8)	0
Within 30 days after any vaccine injections	0	0	(0 ; 2.4)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0	0	0	(0 ; 4.8)	0
Within 30 days after vaccine injections at 2 months of age	0	0	(0 ; 2.4)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0	0	0	(0 ; 4.8)	0
Within 30 days after vaccine injections at 3 months of age	0	0	(0 ; 2.4)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0	0	0	(0 ; 4.8)	0
Within 30 days after vaccine injections at 4 months of age	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Within 30 days after vaccine injections at 4.5 months of age	0	0	(0 ; 2.4)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0	0	0	(0 ; 4.8)	0
Within 30 days after vaccine injections at 6 months of age	0	0	(0 ; 2.4)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0	0	0	(0 ; 4.8)	0
Within 30 days after vaccine injections at 12 months of age	0	0	(0 ; 2.4)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0	0	0	(0 ; 4.8)	0
During the study	1	0.7	(0 ; 3.7)	1	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0	0	0	(0 ; 4.8)	0

Table 37: All and related AESIs during the study, by seriousness criterion - Overall Safety Analysis Set for Any Dose

	Group 1 (N=201)								Group 2 (N=99)							
	All AESIs				Related AESIs				All AESIs				Related AESIs			
Subjects experiencing at least one AESI:	**n**	**%**	**(95% CI)**	**n AESIs**	**n**	**%**	**(95% CI)**	**n AESIs**	**n**	**%**	**(95% CI)**	**n AESIs**	**n**	**%**	**(95% CI)**	**n AESIs**
AESI	1	0.5	(0 ; 2.7)	1	0	0	(0 ; 1.8)	0	1	1.0	(0 ; 5.5)	1	0	0	(0 ; 3.7)	0
Congenital anomaly or birth defect	0	0	(0 ; 1.8)	0	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 3.7)	0
Significant disability	0	0	(0 ; 1.8)	0	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 3.7)	0
Death	0	0	(0 ; 1.8)	0	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 3.7)	0
Hospitalization	1	0.5	(0 ; 2.7)	1	0	0	(0 ; 1.8)	0	1	1.0	(0 ; 5.5)	1	0	0	(0 ; 3.7)	0
Life threatening	0	0	(0 ; 1.8)	0	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 3.7)	0
Other medically important event	0	0	(0 ; 1.8)	0	0	0	(0 ; 1.8)	0	0	0	(0 ; 3.7)	0	0	0	(0 ; 3.7)	0

	Group 3 (N=150)								Group 4 (N=75)							
	All AESIs				Related AESIs				All AESIs				Related AESIs			
Subjects experiencing at least one AESI:	n	%	(95% CI)	n AESIs	n	%	(95% CI)	n AESIs	n	%	(95% CI)	n AESIs	n	%	(95% CI)	n AESIs
AESI	1	0.7	(0 ; 3.7)	1	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0	0	0	(0 ; 4.8)	0
Congenital anomaly or birth defect	0	0	(0 ; 2.4)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0	0	0	(0 ; 4.8)	0
Significant disability	0	0	(0 ; 2.4)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0	0	0	(0 ; 4.8)	0
Death	0	0	(0 ; 2.4)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0	0	0	(0 ; 4.8)	0
Hospitalization	1	0.7	(0 ; 3.7)	1	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0	0	0	(0 ; 4.8)	0
Life threatening	0	0	(0 ; 2.4)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0	0	0	(0 ; 4.8)	0
Other medically important event	0	0	(0 ; 2.4)	0	0	0	(0 ; 2.4)	0	0	0	(0 ; 4.8)	0	0	0	(0 ; 4.8)	0

2.3.3. Discussion on clinical aspects

MET33 was a phase III, open-label, randomised, parallel-group, active-controlled, multi-centre study planned to descriptively compare the immunogenicity and safety of a 3-dose immunisation schedule of MenACYW (Group1: MenACYW + paediatric vaccines) and a 4-dose immunisation schedule of the comparator meningococcal conjugate vaccine Menveo (Group2: Menveo + paediatric vaccines) when administered concomitantly with routine paediatric vaccines (Prevnar 13, Hexacima, RotaTeq, and M-M-RII) in healthy infants and toddlers aged 2 to 12 months in Mexico, and to describe the immunogenicity and safety of a 3-dose immunisation schedule of MenACYW conjugate vaccine when administered concomitantly with routine paediatric vaccines (Group3: MenACYW + paediatric vaccines and Group4: paediatric vaccines only; Prevnar 13, Pentaxim, ENGERIX-B, and MMR) in healthy infants and toddlers aged 2 to 12 months in the Russian Federation. Hence, a control group for meningococcal vaccination in the Russian Federation is lacking. MenACYW was administered at 2, 6 and 12 months of age. Menveo was administered at 2, 4, 6, and 12 months of age. It is critically noted that no hypotheses testing was planned for the study and that the study followed an open label design, which might influence the reporting of safety events.

Menveo is currently approved in the EU only from the age of 2 years. At submission of the planned type II variation, the MAH should discuss the use of Menveo as comparator vaccine. Furthermore, at the time of variation submission the MAH should justify a possible extrapolation of the concomitant vaccines and schedules used to the European situation (available vaccines and recommended vaccination schedules in the EU).

A total of 300 subjects were enrolled and randomised in Mexico and 190 subjects were enrolled and randomised in the Russian Federation: 200 subjects were enrolled from Mexico and randomised to Group 1, 100 subjects were enrolled from Mexico and randomised to Group 2, 150 subjects were enrolled from the Russian Federation and randomised to Group 3, and 75 subjects were enrolled from the Russian Federation and randomised to Group 4. The overall ratio of male/female subjects was 0.95 in Mexico and 0.92 in the Russian Federation which is acceptable. The mean age (±SD) of subjects enrolled in Mexico was 67.1 (±7.37) days [range: 60 to 90 days]; 72.8 (±8.57) days [range: 60 to 93 days] in the Russian Federation. Hence, the mean age of subjects was comparable between Mexico and the Russian Federation. Of note, the ethnical/geographical origin of subjects varied between the 2 countries. In Mexico (Groups 1 and 2), most of the subjects (81.3%) enrolled were American Indian or of Alaskan Native. The racial origin for the remaining 18.7% subjects was not reported. In the Russian Federation (Groups 3 and 4), all subjects enrolled were White. The possible impact of distinct HLA backgrounds of the native American (Mexico) and White (Russian Federation) individuals as well as the possible impact of geographic differences in serotype distribution on study outcomes should be discussed in the planned Variation.

Immunogenicity

Immunogenicity data for meningococcal and routine pediatric vaccines were presented descriptively. The primary objectives were to describe the vaccine seroprotection to the antigens present in MenACYW conjugate vaccine (Group 1) or *Menveo* (Group 2) when administered concomitantly with routine paediatric vaccines in healthy infants and toddlers in Mexico and to describe the vaccine

seroprotection following MenACYW conjugate vaccine (Group 3) when administered concomitantly with routine paediatric vaccines in the Russian Federation. Primary endpoints were meningococcal serogroups A, C, Y, and W antibody titres ≥ 1:8 measured by hSBA, assessed at 30 days after the last vaccination in the second year of life with MenACYW conjugate vaccine (Group 1 and 3) or Menveo (Group 2).

In Mexico, the percentages of subjects with hSBA antibody titres ≥1:8 at D30 after the last dose were 97.6% for serogroup A, 99.2% for serogroup C, 100.0% for serogroups Y and W in Group 1 (MenACYW conjugate vaccine) and 95.0% for serogroup A, 93.3% for serogroup C, 100.0% for serogroups Y and W in Group 2 (Menveo vaccine). In the Russian Federation, the percentages of subjects with hSBA antibody titres ≥1:8 were 89.6% for serogroup A, 82.3% for serogroup C, 80.2% for serogroups Y and W in subjects who received MenACYW conjugate vaccine (Group 3).

Hence, the majority subjects showed seroprotection after MenACYW conjugate vaccine (in Mexico and the Russian Federation) or *Menveo* vaccine (in Mexico) in the second year of life with overall comparable responder rates between vaccines. According to MAH´s post hoc sensitivity analysis, the lower immunogenicity in the Russian Federation is mainly derived from study site no. 6431007. Reasons for the additional analysis with site exclusion were observed differences in seroprotection rates and GMTs with around 10-fold lower results compared to all other study sites. The analysis excluding the Russian Federation site no. 6431007 showed a higher percentage of subjects with hSBA titres ≥ 1:8, similar to the results observed in Group 1 in Mexico. The additional insight provided by this sensitivity analysis is acknowledged, but the exclusion of site no. 6431007 is not sufficiently justified to conclude on immunogenicity based on this sensitivity analysis.

Regarding the secondary objectives, at D30 after the last vaccination in the infant series at 6 months of age, the hSBA vaccine seroresponse (i.e. for a subject with a pre-vaccination titre < 1:8, the post-vaccination titre must be >= 1:16; for a subject with a pre-vaccination titre >= 1:8, the post-vaccination titre must be at least 4-fold greater than the pre-vaccination titre) in Mexico was higher in subjects who received 2 doses of MenACYW conjugate vaccine (Group 1) than in subjects who received 3 doses of *Menveo* vaccine (Group 2) for serogroups A (84.7% vs 58.0%) and C (100.0% vs 86.4%) and was comparable for serogroups W (98.3% vs 97.5%) and Y (99.4% vs 92.6%) in both groups. In the Russian Federation (Group 3), the seroresponse after MenACYW conjugate vaccine was slightly lower (compared to Mexico) with 70.1% for serogroup A, 94.8% for serogroup C, 87.6% for serogroup Y, and 93.8% for serogroup W, reminiscent of results with the primary endpoint and hSBA GMTs.

At D30 after the last vaccination in the second year of life, the hSBA vaccine seroresponse in Mexico was overall comparable between subjects who received 2 doses of MenACYW conjugate vaccine (Group 1) and subjects who received 3 doses of *Menveo* vaccine (Group 2) for serogroups A (96.8% vs 85.0%), C (99.2% vs 88.3%), Y (100% vs 96.7%), and W (99.2% vs 100%). Hence, the seroresponse following the MenACYW vaccine overall increased slightly after vaccination in the second year of life compared to 6 months of age in Mexico. In the Russian Federation, the hSBA vaccine seroresponse was lower (A: 74.0%, C: 81.3%, Y: 80.2% and W: 79.2%) at D30 after the last vaccination in the second year of life compared to Mexico. Furthermore, the seroresponse in the Russian Federation was lower in the second year of life compared to 6 months of age which is somewhat unexpected.

In Mexico, hSBA GMTs for all 4 serogroups were higher than at baseline (D0) at D30 after the last vaccination of the infant series with either vaccine. The hSBA GMTs were higher in Group 1 (MenACYW conjugate vaccine; A: 71.7, C: 626, Y: 246 and W:340) compared to the Group 2 (*Menveo;* A: 16.7, C: 62.4, Y: 59.8 and W: 95.7). Also, at D30 after the last vaccination in the second year of life, the hSBA GMTs for all serogroups in Group 1 were higher than in Group 2 (A: 145 vs 65.5, C: 897 vs 77, Y: 401 vs 228 and W: 639 vs 242). In the Russian Federation, the hSBA GMTs for all 4 serogroups

were higher than at baseline at D30 after the last vaccination in the infant series. At D30 after the last vaccination in the second year of life, the hSBA GMTs were lower compared to results for group 1 and lower compared to group 2 for serogroups Y and W, but higher compared to group 2 for serogroups A and C (A: 85.4, C: 214, Y: 97.3 and W: 123). With respect to seroresponse and GMTs it is concluded that 3 vaccinations of MenQuadfi until 12 months of age appear to induce a stronger response in antibody titres compared to 4 vaccinations of Menveo in the same time frame and in a comparable population. The interpretation of responses in group 3 are compromised by the lack of a direct comparator but appear lower compared to the same age group in Mexico. It can be speculated whether genetic predisposition of study participants and/or geographic differences in serotype distribution across study sites could have an influence on study outcomes.

The immunogenicity profiles of the investigated routine paediatric vaccines (*Prevnar13, RotaTeq, Hexacima, MMR, Pentaxim, and ENGERIX-B*) were overall comparable when co-administered with a MenACYW conjugate vaccine or *Menveo* vaccine or when administered alone (after the infant series and in the second year of life) in Mexico and the Russian Federation. For instance, MMR vaccination response rates at D30 after vaccination in the second year of life for Groups 1 and 2 in Mexico were Measles: 99.2% vs 100%, Mumps: 100% vs 96.6% and Rubella: 100% vs 100%. In the Russian Federation (Groups 3 and 4), responder rates were Measles: 93.8% vs 88.0%, Mumps: 89.6% vs 90.0% and Rubella: 95.8% vs 94.0%.

According to the CSR, *Prevnar13* was administered in all groups 1-4. However, no immunogenicity data on *Prevnar13* from the Russian Federation (Groups 3 and 4) were found in the current CSR. If possible, these data should be provided with the planned Variation since the comparison: MenACYW + *Prevnar13* vs *Prevnar13* alone is considered of interest for the investigation of this concomitant vaccination.

Safety

The observational safety objectives were to describe the safety profile of MenACYW conjugate vaccine and *Menveo* when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers in Mexico (Group 1 vs Group 2) and the Russian Federation (Group 3) and to describe the safety profile of routine pediatric vaccines in Mexico (Groups 1 and 2) and the Russian Federation (Groups 3 and 4).

Immediate unsolicited systemic AEs were collected within 30 minutes after each vaccination. Other unsolicited AEs were evaluated up to D30 after each vaccination. Solicited AE information (injection site reactions and systemic reactions) were collected from D0 to D07 after each vaccination. SAEs and AESIs were collected throughout the study. These measurements are considered appropriate. The discussion on safety data below refers to the overall safety analysis set. Individual safety analysis sets at 2, 3, 4, 4.5, 6 and 12 months of age will not be discussed in detail, as data do not refer to a licensed population (all subjects are below 12 years of age, have received at least two meningococcal vaccinations against serogroups A, C, Y and W before the age of 12 months or have not received any meningococcal vaccinations against serogroups A, C, Y and W during the study) and the submission in accordance with Article 46 of Regulation (EC) No. 1901/2006, as amended, does not address any extension of the current indication for MenQuadfi to vaccinate healthy infants. It is further critically noted that the study followed an open label design, which might influence the reporting of safety events.

Mexico

The safety profile of MenACYW conjugate vaccine was roughly comparable to that of *Menveo* when administered concomitantly with routine paediatric vaccines, but the rate of reporting was mostly

higher for group 1 compared to group 2, except for grade 3 events, which were reported more frequently by subjects that have received *Menveo*. For instance, the percentages of subjects who reported at least 1 solicited reaction within 7 days after vaccination were 89.5% (179/200) in Group 1 and 76.8% (76/99) in Group 2, and 20.0% (40/200) in Group 1 and 21.2% (21/99) in Group 2 reported at least 1 Grade 3 solicited reaction. The percentages of subjects who reported at least 1 solicited injection site reaction were 78.0% (156/200) in Group 1 and 69.7% (69/99) in Group 2, and 12.0% (24/200) in Group 1 and 14.1% (14/99) in Group 2 reported at least one Grade 3 solicited injection site reaction. Specifically, the percentages of subjects who reported at least 1 solicited injection site reaction at the MenACYW/Menveo injection site were 64.5% (129/200) and 63.6% (63/99), respectively. Also the safety profile of solicited injection site reactions after routine paediatric vaccines was roughly comparable between vaccine groups, but with slightly higher frequencies in group 1. For instance, the percentages of subjects who reported at least 1 solicited injection site reaction at the *Prevnar13* vaccine site were 67.0% (134/200) in Group 1 and 59.6% (59/99) in Group 2. The most frequently reported solicited injection site reactions after MenACYW in Group 1 were injection site tenderness reported by 60.5% (121/200) of subjects followed by injection site erythema (26.0% [52/200] of subjects) and injection site swelling (12.0% [24/200] of subjects) Similarly, after *Menveo* the most frequently reported solicited injection site reactions in Group 2 were also injection site tenderness, reported by 60.6% (60/99) of subjects followed by injection site erythema (13.1% [13/99] of subjects) and injection site swelling (9.1%[9/99] of subjects). Hence, erythema occurred about twice as frequently after MenACYW compared to *Menveo*, which should be anticipated for subjects following the depicted vaccination strategy with *MenQuadfi*, compared to the scheme with Menveo in group 2. For either vaccine most of the injection site reactions were Grade 1 or 2 and resolved within 1-3 days of occurrence.

Comparable to the pattern for reported frequencies for local reactions, the percentages of subjects reporting at least one solicited systemic reaction were 81.5% (163/200) in Group 1 and 70.7% (70/99) in Group 2, and 11.5% (23/200) in Group 1 and 12.1% (12/99) in Group 2 reported at least one Grade 3 solicited systemic reaction. The most frequently reported solicited systemic reactions were irritability, reported by 67.0% (134/200) of subjects in Group 1 and 58.6% (58/99) subjects in Group 2 followed by abnormal Crying (58.5% [117/200] in Group 1 and 50.5% (50/99) in Group 2). Fever (42.2% [84/199] subjects in Group 1 and 33.7% [33/98] subjects in Group 2), drowsiness (40.0% [80/200] subjects in Group 1 and 36.4% [36/99] subjects in Group 2), lost appetite (36.0% [72/200] subjects in Group 1 and 33.3% [33/99] subjects in Group 2), and vomiting (19.5% [39/200] subjects in Group 1 and 11.1% [11/99] subjects in Group 2) were also commonly reported and all with a mildly higher frequency for group 1. The percentages of subjects reporting at least one Grade 3 solicited systemic reaction were 11.5% (23/200) in Group 1 and 12.1% (12/99) in Group 2. Most of the solicited systemic reactions were Grade 1 or 2 and resolved within 1-3 days of occurrence.

Taken together, solicited systemic reactions occurred numerically more often after MenACYW compared to Menveo. For the overall safety analysis set is to be noted that subjects in group 2 received 1 additional vaccination (with Menveo at 4 months of age) compared to subjects in group 1, which might have an effect on reporting rates. Thus, it can be concluded that *MenQuadfi* appears slightly more reactogenic compared to *Menveo* in infants and toddlers, which might be related to the total lower content of Neisseria meningitidis polysaccharide and/or the difference in conjugated proteins (tetanus toxoid carrier protein for *MenQuadfi* and Corynebacterium diphtheriae CRM 197 protein for Menveo).

No immediate unsolicited AEs or ARs were recorded within 30 minutes of any vaccination in any group.

The percentage of subjects reporting at least 1 unsolicited non-serious AE (between D0 and D30) was comparable between Group 1 and Group 2 (49.8% in Group 1 and 47.5% in Group 2). Unsolicited non-serious AEs were mainly reported in the following SOCs: "Infections and Infestations" (43.3% [87/201]; mainly nasopharyngitis), "Gastrointestinal Disorders" (8.0% [16/201]; mainly diarrhoea), and "General Disorders and Administration Site Conditions" (7.0% [14/201]; mainly injection site haematoma) in Group 1 and "Infections and Infestations" (34.3% [34/99]; mainly nasopharyngitis), "General Disorders and Administration Site Conditions" (17.2% [17/99]; mainly injection site haematoma), and "Gastrointestinal Disorders" (12.1% [12/99]; mainly diarrhoea) in Group 2. The percentage of subjects who reported at least 1 Grade 3 unsolicited non-serious AE was 3.0% (6/201) in Group 1. No subjects in Group 2 reported any Grade 3 unsolicited non-serious AEs. The percentage of subjects reporting at least 1 unsolicited non-serious AR (between D0 and D30) was comparable between Group 1 (2.0% [4/201]) and Group 2 (2.0% [2/99]). All unsolicited non-serious ARs were Grade 1 or Grade 2. Most of the unsolicited non-serious ARs lasted for up to 7 days. Unsolicited non-serious ARs were mainly reported in the SOC "General Disorders and Administration Site Conditions" in both groups (2.0% [4/201] in Group 1 and 2.0% [2/99] in Group 2; mainly injection site haemorrhage and injection site haematoma). No concerns arise from reported unsolicited ARs.

No deaths were reported in the Mexican cohort. No subjects in Groups 1 or 2 were discontinued from the study due to an AE. However, seven subjects experienced at least 1 SAE during the study period: 2.0% (4/201) subjects in Group 1 and 3.0% (3/99) subjects in Group 2. The SAEs in Group 1 were seizure (1), pneumonia (2) and Head injury (1). The SAEs in Group 2 were bronchiolitis (2) and febrile seizure (1). Hence, respiratory tract infections were the most frequent SAE in both groups. The percentages of subjects who reported at least 1 AESI were 0.5% (1/201; grade 3 seizures) in Group 1 and 1.0% (1/99; grade 3 febrile convulsions) in Group 2. None of the SAEs or AESIs was considered related to vaccination, which is reassuring and can be followed based on provided narratives. A total of 190 (95.0%) subjects in Group 1 and 92 (92.0%) subjects in Group 2 completed the study, indicating a high and comparable vaccination acceptance for MenACYW and MENVEO vaccines.

Russian Federation

The percentages of subjects who reported at least 1 solicited reaction were 42.7% (64/150) in Group 3 and 45.3% (34/75) in Group 4, and 0.7% (1/150) in Group 3 reported at least 1 Grade 3 solicited reaction. No Grade 3 solicited reaction was reported in Group 4.

The percentages of subjects who reported at least 1 solicited injection site reaction were 22.0% (33/150) in Group 3 and 16.0% (12/75) in Group 4. No Grade 3 injection site reactions were reported in Groups 3 and 4. The percentage of subjects who reported at least 1 solicited injection site reaction at the MenACYW conjugate vaccine site was 11.4% (17/149). The percentages of subjects who reported at least 1 solicited injection site reaction after a routine paediatric vaccine were similarly low but comparable between Groups 3 and 4 (e.g. *Prevnar13* vaccine site: 8.7% [13/150] vs 10.7% [8/75]). The most frequently reported solicited injection site reactions after MenACYW in Group 3 were injection site erythema, reported by 7.4% (11/149) of subjects followed by injection site tenderness (6.0% [9/149] of subjects) and injection site swelling (4.0% [6/149] of subjects). Most of the injection site reactions resolved within 1-3 days of occurrence.

The percentages of subjects reporting at least one solicited systemic reaction were 34.0% (51/150) in Group 3 and 38.7% (29/75) in Group 4, and 0.7% (1/150) in Group 3 reported at least one Grade 3 solicited systemic reaction. No Grade 3 systemic reactions were reported in Group 4. The most frequently reported solicited systemic reactions in Group 3 were drowsiness, reported by 22.0% (33/150) subjects followed by irritability that was reported by 21.3% (32/150) of subjects. The most frequently reported solicited systemic reactions in Group 4 were irritability, reported by 26.7% (20/75)

subjects followed by drowsiness (22.7% [17/75] of subjects). Lost Appetite (17.3% [26/150] subjects in Group 3 and 14.7% [11/75] subjects in Group 4), abnormal crying (12.0% [18/150] subjects in Group 3 and 8.0% [6/75] subjects in Group 4), and fever (7.4% [11//149] subjects in Group 3 and 8.0% [6/75] subjects in Group 4) were also common. Most of the solicited systemic reactions resolved within 1-3 days of occurrence. Hence, overall comparable safety profiles were observed for Groups 3 and 4.

No immediate unsolicited AEs or ARs were recorded within 30 minutes of any vaccination in any group.

The percentage of subjects reporting at least 1 unsolicited non-serious AE was comparable between Group 3 and Group 4 (10.0% [15/150] in Group 3 and 8.0% [6/75] in Group 4). All the unsolicited non-serious AEs were of Grade 1 or Grade 2. Unsolicited non-serious AEs were mainly reported in the following SOCs: “Infections and Infestations” (6.0% [9/150] subjects in Group 3 and 5.3% [4/75] subjects in Group 4; mainly rhinitis) and “Gastrointestinal Disorders” (2.7% [4/150] subjects in Group 3 and 2.7% [2/75] subjects in Group 4). There were no unsolicited non-serious ARs reported in Groups 3 and 4 within 30 days after vaccine injection.

No deaths were reported in the Russian cohort. No subjects in Groups 3 or 4 were discontinued from the study due to an AE. Six subjects experienced at least 1 SAE during the study period: 2.7% (4/150) subjects in Group 3 and 2.7% (2/75) subjects in Group 4. The SAEs in Group 3 were viral enterocolitis (2), atonic seizure (1) and COVID-19 (1). Hence, infections and seizures were reported as most frequent SAEs after MenACYW as for the Mexican cohort. The SAEs in Group 4 were bone fracture (1) and pneumonia (1). The percentage of subjects who reported at least 1 AESI was 0.7% (1/150) in Group 3 (grade 1 atonic seizure). None of the SAEs or AESIs was considered related to vaccination which is reassuring and can be followed based on provided narratives. A total of 148 (98.7%) subjects in Group 3 and 75 (100.0%) subjects in Group 4 completed the study, indicating a high vaccination acceptance.

Of note, the observed frequency of AEs reported in the Russian Federation was generally substantially lower than in Mexico. According to the MAH´s literature analysis, this pattern can be regularly observed in clinical studies of paediatric vaccines in the Russian Federation, which is acknowledged. However, reasons for this discrepancy are not entirely clear.

Overall, the administration of MenACYW conjugate vaccine as evaluated in study MET33 yielded no significant or unexpected safety concerns in healthy infants and toddlers aged 2 to 12 months in Mexico and the Russian Federation.

3. Rapporteur’s overall conclusion and recommendation

The study population of MET33 is not covered by the EU Marketing Authorisation of MenQuadfi, which is currently indicated from the age of 12 months and older.

The purpose of MET33 was to demonstrate that the safety profile and immunogenicity of the 3-dose series of MenACYW conjugate vaccine (MenQuadfi) is similar to that of a 4-dose series of Menveo when starting immunisation at 2 months of age and administered concomitantly with routine paediatric vaccines given to healthy infants and toddlers in Mexico, and to demonstrate that the safety profile and immunogenicity of MenACYW conjugate vaccine is similar when given concomitantly with routine paediatric vaccines given to healthy infants and toddlers in the Russian Federation. It is critically noted that the study design does not address any possible consequence of the concomitant vaccination with routine paediatric vaccines on the immunogenicity profile of MenQuadfi (i.e., MenQuadfi alone vs. MenQuadfi + routine vaccines). One study arm with a sequential administration of MenQuadfi and

routine vaccines (that would still allow to provide the routine vaccination to all children) could have provided further insight in this aspect. However, the adequacy of the study design to investigate the appropriateness of concomitant vaccination will need to be assessed in the intended future application.

The submitted results of study MET33 comprised descriptive immunogenicity data for MenQuadfi, the comparator vaccine Menveo and concomitant paediatric vaccines as well as safety data sets summarizing AEs that occurred during the study. Overall, MenQuadfi showed a slightly higher immunogenicity than Menveo. Routine paediatric vaccines showed comparable immunogenicity when administered concomitantly with MenQuadfi or Menveo in healthy infants and toddlers. The safety profile of MenQuadfi was roughly comparable to Menveo. However, it is critically noted that no hypotheses testing was planned for the study and that the study followed an open label design, which might influence the reporting of safety events.

The adequacy of Menveo as comparator vaccine is questionable as Menveo is not licensed for the respective age group in the EU. This aspect requires further elaboration for any future variation application. Similarly, the use of administered concomitant vaccines should be justified based on EU standards (i.e., licensure of vaccines used and vaccine schedule). Furthermore, serious adverse events (especially those related to respiratory and gastrointestinal infections as well as seizures) should be discussed in detail once all data of the clinical program in subjects <12 years become available.

Study MET33 is part of the MenQuadfi Paediatric Investigational Plan EMEA-001930-PIP01-16-M04). The MAH´s plan is to complete all the ongoing paediatric clinical studies MET33, MET41, MET42, MET52, MET58, MET61 covering 6 weeks to 12 months population prior to submit all the data together under a type II variation with Product Information update to support the extension of indication for use of MenQuadfi in individuals from the age of 6 weeks and older (planned submission Q1 2025 in the EU).

☒ Fulfilled:

No regulatory action required.

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

The studies should be listed by chronological date of completion:

Clinical studies

Product Name:

MenQuadfi

Active substance:

Neisseria meningitidis group A polysaccharide

Neisseria meningitidis group C polysaccharide

Neisseria meningitidis group Y polysaccharide

Neisseria meningitidis group W polysaccharide

Conjugated to tetanus toxoid carrier protein

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