EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 June 2026
EMADOC-1700519818-3191178
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on extension of indication

Invented name: MenQuadfi

Common name: Meningococcal Group A, C, W and Y conjugate vaccine

Procedure No. EMA/VR/0000281377

Marketing Authorisation Holder (MAH): Sanofi Winthrop Industrie

Note

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

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List of abbreviations

Ab	antibody
AESI	adverse events of special interest
AE	adverse event
AR	adverse reaction
CBER	Center for Biologics Evaluation and Research
CFR	case fatality rate
CHMP	Committee for Medicinal Product for Human Use
CI	confidence interval
COVID-19	Coronavirus disease 19
CSR	clinical study report
CTD	common technical document
D	day
DTaP	diphtheria, tetanus, and acellular pertussis
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
GBS	Guillain-Barré syndrome
GMT	geometric mean titre
HB or Hep B	hepatitis B
Hep A	hepatitis A
Hib	*Haemophilus influenzae* type b
HIV	human immunodeficiency virus
hSBA	serum bactericidal assay using human complement
ICH	International Council for Harmonization
IgG	immunoglobulin G
IM	intra-muscular
IMD	invasive meningococcal disease
IPV	inactivated poliovirus
ISS	Integrated Summary of Safety
MCV4	Meningococcal Conjugate Vaccine, Quadrivalent
MenB	meningococcal group B
MMR	measles, mumps, and rubella
N. meningitidis	*Neisseria meningitidis*
NI	non-inferiority
PCV13	pneumococcal 13-valent conjugate vaccine
PCV10	pneumococcal 10-valent conjugate vaccine
PEP	primary endpoint
PK	pharmacokinetic
PP	Per-protocol
PPAS	Per-protocol analysis set
PRAC	Pharmacovigilance Risk Assessment Committee
PRP	polyribisyl-ribitol polysaccharide
PS	polysacchrides
PSP	Pediatric Study Plan
PT	pertussis toxin

rSBA	serum bactericidal assay using rabbit complement
RV5	pentavalent rotavirus vaccine
SAE	serious adverse event
SafAS	Safety Analysis Set
SAP	Statistical Analysis Plan
SEP	secondary endpoint
UK	United Kingdom
US	United States
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Sanofi Winthrop Industrie submitted to the European Medicines Agency on 25 June 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication for MenQuadfi to include the active immunisation of patients from 6 weeks of age based on final results from study MET58 and additional supportive clinical studies. Study MET58 is a Phase 3, 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. As a consequence, sections 4.1, 4.2, 4.5, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. An updated Risk Management Plan (RMP) version 4.0 is also included.

The variation requested amendments to the Summary of Product Characteristics, Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0349/2024 on the agreement of a paediatric investigation plan (PIP) for prevention of invasive meningococcal disease.

At the time of submission of the application, the PIP P/0349/2024 had been completed.

The PDCO issued on 28 March 2025 a positive opinion on compliance for PIP P/0349/2024.

All studies/measures contained in the PIP were checked for compliance:

Agreed studies/measures (study identifier)	**Description**
Study 1 (MET50)	An open-label, randomized, parallel-group, controlled, multi-centre study to evaluate the immunogenicity and safety profile of a single dose of MenACYW conjugate vaccine {…} study
Study 2 (MET54)	A randomized, active-controlled, open-label study to evaluate the immunogenicity and safety profile of a single dose of MenACYW conjugate vaccine when given alone compared to that of a licensed meningococcal group A, C, W-135 and Y conjugate vaccine (Nimenrix) in 12 to 23 months old paediatric subjects.
Study 3 (MET51)	A modified double-blind, randomized, parallel-group, active-controlled, multi-centre trial to compare the immunogenicity and describe the safety of

Agreed studies/measures (study identifier)	Description
	a single dose of MenACYW conjugate vaccine to a single dose of licensed quadrivalent meningococcal polysaccharide groups A, C, W-135, and Y conjugate vaccine (MenACWY-Tetanus Toxoid [TT], Nimenrix) in paediatric subjects from 12 to less than 24 months old in the European Union (EU) who were either meningococcal vaccine naïve or had received monovalent MenC vaccination during infancy.
Study 4 (MET57)	Open-label, randomized, parallel-group, active-controlled, multi-centre study to describe the immunogenicity and safety of a single dose of MenACYW conjugate vaccine when administered alone and when administered concomitantly with other paediatric vaccine(s) in paediatric subjects from 12 to less than 24 months old.
Study 5 (MET35)	A double-blind, randomized, parallel-group, active-controlled, trial to evaluate the immunogenicity and describe the safety of MenACYW conjugate vaccine compared to Meningococcal (Groups A, C, Y and W-135) Diphtheria Conjugate Vaccine (Menveo) in paediatric subjects 2 to 9 years of age in the United States.
Study 12 (MET43)	Modified double-blind, randomized, parallel-group, active-controlled, multi-centre study to evaluate immune lot consistency of MenACYW conjugate vaccine, evaluate the immune non-inferiority versus Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine (Menactra), and describe the safety and additional immunogenicity of study vaccines in paediatric patients 10 to less than 18 years old.
Study 13 (MET56)	Double-blind, randomized, parallel-group, active-controlled, multi-centre trial to compare the immunogenicity and describe the safety of a booster dose of MenACYW conjugate vaccine compared to Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine (Menactra) in paediatric subjects from 15 to less than 18 years old.
Study 14, (MET62)	Open-label, multi-centre study to describe the immune persistence of the priming dose and describe the immunogenicity and safety of a booster dose of MenACYW conjugate vaccine in children in Finland who had been vaccinated 3 years earlier
Study 15, (MET59)	Open-label, multi-centre study to evaluate the immune persistence of the priming dose and describe the immunogenicity and safety of a booster dose of MenACYW conjugate vaccine, when co-administered along with MenB vaccines in adolescents (and adults) in USA who had been vaccinated 5 years earlier as adolescents with either MenACYW conjugate vaccine or Meningococcal (Groups A, C, Y and W-135) Diphtheria Conjugate Vaccine (Menveo) as part of the MET50 study (Study 1).
Study 6 (MET52)	Open-label, randomized, parallel-group, active-controlled, multi-centre study to evaluate the immunogenicity and describe the safety of MenACYW conjugate vaccine when administered concomitantly with Men B vaccine

Agreed studies/measures (study identifier)	Description
	and other routine paediatric vaccines as part of the National Immunization Schedule in the 2nd year of life to healthy paediatric subjects in the United Kingdom; (study MET52).
Study 7 (MET58)	Partially modified double-blind (open-label for some of the vaccines/study groups), randomized, parallel-group, active-controlled, multi-centre study to compare the immunogenicity and describe the safety of MenACYW conjugate vaccine to a licensed quadrivalent meningococcal polysaccharide groups A, C, W-135, and Y conjugate vaccine (Nimenrix) when administered concomitantly with routine paediatric vaccines to healthy paediatric subjects from 6 weeks old in EU
Study 8 (MET42)	Partially modified double-blind, randomized, parallel-group, active-controlled, multi-centre study to compare the immunogenicity and describe the safety of MenACYW conjugate vaccine and Meningococcal (Groups A, C, Y and W-135) Diphtheria Conjugate Vaccine (Menveo) when administer ed concomitantly with routine paediatric vaccines to paediatric subjects from 6 weeks old in the United States
Study 9 (MET41)	Modified double-blind, randomized, parallel-group, active-controlled, study to describe the safety of MenACYW conjugate vaccine when administered concomitantly with routine paediatric vaccines given to healthy infants and toddlers in the United States and Puerto Rico to describe the safety profile of MenACYW conjugate vaccine and Menveo when administered concomitantly with routine paediatric vaccines in healthy infants and toddlers
Study 10 (MET33)	Open-label, randomized, parallel-group, active-controlled, multi-centre study to describe the immunogenicity and safety of a 3-dose immunization schedule of MenACYW conjugate vaccine or a 4-dose immunization schedule of a licensed quadrivalent meningococcal conjugate vaccine (Menveo) when administered concomitantly with routine paediatric vaccines in healthy infants and toddlers in Mexico and to describe the immunogenicity and safety of a 3-dose immunization schedule of MenACYW conjugate vaccine when administered concomitantly with routine paediatric vaccines in healthy infants and toddlers in the Russian Federation
Study 11 (MET61)	Modified double-blind, randomized, parallel-group, active-controlled, multi-centre study to compare the immunogenicity and describe the safety of MenACYW conjugate vaccine and Menveo or Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine (Menactra) when administered concomitantly with or without routine paediatric vaccines to paediatric subjects 6 months to 19 months old, in the United States

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 23 February 2017 and 26 January 2023. The Scientific Advice pertained to clinical aspects and in relation to paediatric development of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Daniela Philadelphy

Timetable	Actual dates
Submission date	25 June 2025
Start of procedure:	19 July 2025
CHMP Rapporteur's preliminary assessment report circulated on:	12 September 2025
PRAC Rapporteur's preliminary assessment report circulated on:	19 September 2025
Joint Rapporteur's updated assessment report circulated on:	09 October 2025
Request for supplementary information adopted by the CHMP on:	16 October 2025
MAH's responses submitted to the CHMP on:	22 January 2026
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	27 February 2026
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	04 March 2026
PRAC RMP advice and assessment overview adopted by PRAC	12 March 2026
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	19 March 2026
Request for supplementary information adopted by the CHMP on:	26 March 2026
MAH's responses submitted to the CHMP on:	22 April 2026
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	26 May 2026
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	28 May 2026

Timetable	Actual dates
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	18 June 2026
CHMP opinion:	25 June 2026

2. Scientific discussion

2.1. Introduction

On 18th November 2020, a marketing authorisation valid throughout the European Union for MenQuadfi, a meningococcal vaccine against invasive meningococcal disease (IMD) caused by Neisseria meningitidis serogroups A, C, W, and Y, was issued.

The purpose of the current Type II variation is the extension of the indication to include individuals starting from the age of 6 weeks. Currently, MenQuadfi is indicated for individuals from the age of 12 months and older.

IMD is a serious illness caused by the bacterium *N. meningitidis*, a Gram-negative diplococcus found exclusively in humans. Symptoms of IMD may include headache, fever, photophobia, stiff neck, lethargy, myalgia, and a characteristic petechial or purpuric rash. It can be a life-threatening disease, which clinically presents as septicaemia and meningitis. Seizures occur in approximately 20% of patients. In survivors, IMD can result in severe sequelae in 10% to 20% of patients despite appropriate therapy, with potentially life-changing consequences.

According to aggregate EU/EEA surveillance data in the Invasive meningococcal disease Annual Epidemiological Report for 2022, published on 22 April 2024 (for the period 2018-2022) infants are the most impacted by meningococcal diseases. The highest incidence of IMD occurred in infants less than 1 year old.

The virulence of *Neisseria meningitidis* is mostly based on the biochemical structure of capsular polysaccharides. So far 12 distinct meningococcal serogroups have been classified, with serogroups A, B, C, W, X and Y being responsible for most cases of meningococcal disease. Dynamics of meningococcal transmission, acquisition, and carriage in humans are a major influence on the incidence and likelihood of meningococcal disease and vary world-wide greatly among regions. The European population is mostly affected by serogroup B, but also C and Y have been reported. At present, the best prevention known against meningococcal disease is the up-front immunisation with vaccines targeting the relevant serogroups.

Meningococcal vaccines induce the production of antibodies specific to the capsular polysaccharides of *N. meningitidis* serogroups, which protect against meningococcal diseases via complement mediated bactericidal activity.

By the time this assessment started in 2025, in the EU, the only quadrivalent meningococcal vaccine against serogroups A, C, W, and Y approved for individuals from the age of 6 weeks to below 12 months (and thus the population with the highest disease burden) is Nimenrix. Menveo, also a quadrivalent meningococcal vaccine against serogroups A, C, W, and Y, is only authorised for administration to children starting from 2 years of age.

2.1.1. The development programme/compliance with CHMP guidance/scientific advice

The MAH twice requested scientific advice regarding the use of their MenACWY-TT vaccine (MenQuadfi) in individuals from 6 weeks to 12 months of age (EMEA/H/SA/3131/1/FU/1/2017/II (Report date: 23.02.2017), and EMA/SA/0000114629 (Report date: 26.01.2023)).

In scientific advice EMEA/H/SA/3131/1/FU/1/2017/II, the MAH was asked to identify the minimal effective regimen instead of including multiple dosing regimens in the SmPC for flexibility. It was commented that none of the planned studies at the time directly compared dosing regimens, and that a cross-study comparison is not considered viable to enable a reliable assessment of how many infant doses are needed when starting early or later within the first year of life. Therefore, it was recommended to conduct direct comparative studies for 1+1 MenACWY-TT, 2+1 MenACWY-TT, and 2+1 Nimenrix. Further, it was recommended to conduct the studies using Infanrix hexa (hexavalent combined DTaP-HBV-IPV-Hib vaccine) and Synflorix (10-valent pneumococcal conjugate vaccine, PCV10) as concomitant vaccines, as they are not known to have an influence on Nimenrix. Concerns regarding the co-administration with Prevenar 13 (PCV13) were voiced, as co-administration of multiple polysaccharide-protein conjugates influences the immune response and therefore complicates the non-inferiority assessment vs. Nimenrix. It was critically remarked that none of the planned studies planned for evaluation of antibody persistence.

The proposed studies MET58 and MET33 did not follow the posology for Nimenrix, and any deviation would have required open-label designs. As PEP, the percentage of subjects achieving hSBA ≥1:8 after the last infant dose was considered appropriate. Evaluating this parameter as PEP after the booster dose was discouraged due to the expectation of anamnestic immune response, which would have decreased the sensitivity of the study to measure non-inferiority.

Regarding study MET52, it was commented that the results from this design could not support a recommendation for co-administration of MenACWY-TT and MenB, as a co-administration at 12 and 18 months was considered to require a separate study including vaccine-naïve subjects receiving MenACWY-TT, MenB or in combination, all receiving the same concomitant vaccines (as allowed in the Bexsero SmPC). Similarly, to support co-administration in infancy, subjects were proposed to be randomised to MenACWY-TT, Bexsero or in combination, with immune responses assessed one month after the final dose. The posology for Bexsero would have needed to align with the approved schedule for the studied age group. In countries where MenB was already approved, a staggered design could have been employed to avoid conflicts with national recommendations.

In scientific advice EMA/SA/0000114629, the MAH was asked to submit trial data for studies investigating a 3+1 dosing scheme, and was informed that Menveo is not considered a valid comparator to support the 1+1 posology in children aged 6 to 12 months (Study MET52), as Menveo is not authorised in the EU in children <2 years, and because the development programme should provide direct comparisons between regimens to demonstrate how many priming doses are needed in the first year of life to achieve comparable immune responses to those elicited by Nimenrix after two doses.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Identifier/ Location of CSR	Study Title, Study Design, and Control	Objectives	Planned Sample Size / Population / Age at Enrollment / Study Groups
Immunogenicity and/or Safety Studies with the Final Formulation - Studies that Constitute the Clinical Database Presented in this CTD Addendum			
MET58	**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** Phase III, partially modified double-blind (open-label for some of the vaccines / study groups), randomised, parallel-group, active-controlled, multi-center study. **Schedule:** Dose 1 at 6 weeks - 2 months Dose 2 at 4 months Dose 3 at 12 – 18 months **Control:** Nimenrix **Concomitant vaccines:** DTaP-IPV-HB-Hib, Prevenar 13, Synflorix, M- M- RVAXPRO	Primary Objective: To demonstrate the non-inferiority (NI) of the antibody response against meningococcal serogroups A, C, W, and Y following the administration of a 3-dose series of MenACYW conjugate vaccine compared to a 3-dose series of Nimenrix when each vaccine was administered concomitantly with routine pediatric vaccines (PCV10 and hexavalent vaccine) to infants and toddlers from 6 weeks to 18 months old (Group 1 versus Group 2) Secondary Objectives: 1) To demonstrate the NI of the antibody response against meningococcal serogroups A, C, W, and Y following the administration of 2 doses in infancy of MenACYW conjugate vaccine compared to 2 doses in infancy of Nimenrix when each vaccine was administered concomitantly with routine pediatric vaccines (PCV10 and hexavalent vaccine) (Group 1 versus Group 2) 2) To describe the antibody responses against meningococcal serogroups A, C, W, and Y when MenACYW conjugate vaccine is administered in a 3-dose series concomitantly with the routine pediatric vaccines (Group 3) 3) To describe the antibody responses against the antigens of the routine pediatric vaccines administered in a 3-dose series concomitantly with MenACYW conjugate vaccine or Nimenrix (Groups 1, 2, and 3) 4) To describe the antibody responses against meningococcal serogroups A, C, W, and Y measured by serum bactericidal assay using human complement (hSBA) when MenACYW conjugate vaccine or Nimenrix was administered in a 3-dose series concomitantly with PCV10 and other routine pediatric vaccines (Groups 1 and 2) 5) To describe the antibody responses against meningococcal serogroups A, C, W, and Y measured by hSBA when MenACYW conjugate vaccine was administered in a 4-dose series concomitantly with PCV13 and other routine pediatric vaccines (Group 4) To describe the antibody responses against the antigens of the routine pediatric vaccines administered with MenACYW conjugate vaccine administered in a 4-dose series concomitantly (Group 4) Safety Objective: To describe the safety profile of MenACYW conjugate vaccine and Nimenrix when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers	1652 healthy infants aged 2 months (6 to 12 weeks) who were meningococcal, pneumococcal, diphtheria, tetanus, pertussis, *Heamophilus influenzae* type B, polio, measles, mumps, rubella, and hepatitis B vaccine-naïve in Finland, Sweden, Poland, Spain, and Czech Republic) **Study Groups:** Group 1: MenACYW conjugate vaccine (2+1 regimen) + PCV10 + Hexavalent vaccine +/- MMR vaccine (n=716) Group 2: Nimenrix (2+1 regimen) + PCV10 + Hexavalent vaccine +/- MMR vaccine (n=716) Group 3: MenACYW conjugate vaccine (2+1 regimen) + PCV13 + Hexavalent vaccine +/- MMR vaccine (n=110) Group 4: MenACYW conjugate vaccine (3+1 regimen) + PCV13 + Hexavalent vaccine +/- MMR vaccine (n=110)

Study Identifier/ Location of CSR	Study Title, Study Design, and Control	Objectives	Planned Sample Size / Population / Age at Enrollment / Study Groups
MET33	**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** Open-label, randomised, parallel-group, active-controlled study to describe the immunogenicity and safety of a 3-dose immunisation schedule of MenACYW conjugate vaccine or a 4-dose immunisation schedule of Menveo when administered concomitantly with routine pediatric vaccines 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 pediatric vaccines in healthy infants and toddlers aged 2 to 12 months in the Russian Federation. **Schedule:** Dose 1 at 2 – 3 months Dose 2 – at 6 months Dose 3 – at 12 months ***Mexico:*** **Control**: Menveo **Concomitant Vaccines:** Prevnar 13 at 2, 4, 6, and 12 months of age Hexacima at 2, 4, 6, and 12 months of age RotaTeq at 2, 4, and 6 months of age	Co-Primary Objectives: 1) To describe the vaccine seroprotection (antibody titre ≥ 1:8) to the antigens (meningococcal serogroups A, C, W and Y) present in MenACYW conjugate vaccine or Menveo measured by serum bactericidal assay using human complement (hSBA), for Groups 1 and 2, when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers in Mexico 2) To describe the vaccine seroprotection (antibody titre ≥ 1:8) to the antigens (meningococcal serogroups A, C, W, and Y) present in MenACYW conjugate vaccine measured by hSBA, for Group 3, when administered concomitantly with routine pediatric 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, W, and Y) 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 pediatric vaccines in healthy infants and toddlers in Mexico 2) To describe the hSBA vaccine seroresponse to the antigens (meningococcal serogroups A, C, W, and Y) for Group 3, 30 days after the last vaccination of the infant series (Dose 2 of MenACYW conjugate vaccine), when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers in the Russian Federation 3) To describe the immunogenicity profile of routine pediatric 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, W, and Y when MenACYW conjugate vaccine and Menveo are administered concomitantly with routine pediatric vaccines in Mexico and the Russian Federation (Groups 1, 2, and 3) 5) To describe the antibody titres to the antigens (meningococcal serogroups A, C, W, and Y) 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 pediatric vaccines in a subset of participants (100 participants in Group 1 and 50 participants in Group 2) in Mexico 6) To describe the antibody titres to the antigens (meningococcal serogroups A, C, W, and Y) 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 pediatric vaccines in a subset of participants (100 participants in Group 3) in the Russian Federation 7) To describe the antibody titres to the antigens (meningococcal serogroups A, C, W, and Y) 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 pediatric vaccines in a subset of participants (100 participants in Group 1 and 50 participants in Group 2) in Mexico 8) To describe the antibody titres to the antigens (meningococcal serogroups A, C, W, and Y) present	300 healthy meningococcal vaccine-naïve infants aged 2 months in Mexico and 225 healthy meningococcal vaccine-naïve infants aged 2 months in the Russian Federation **Study Groups:** ***Mexico*** 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 Group 2: Menveo at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age ***The Russian Federation*** 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 Group 4: Routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age

Study Identifier/ Location of CSR	Study Title, Study Design, and Control	Objectives	Planned Sample Size / Population / Age at Enrollment / Study Groups
	MMR-II at 12 months of age ***The Russian Federation:*** **Control:** No meningococcal control vaccine **Concomitant Vaccines:** Prevnar 13 at 2 and 4.5 months of age Pentaxim at 3, 4.5, and 6 months of age Engerix-B at 6 months of age MMR vaccine at 12 months of age	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 pediatric vaccines in a subset of participants (100 participants in Group 3) in the Russian Federation Safety Objectives: 1) 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) 2) To describe the safety profile of MenACYW conjugate vaccine when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers in the Russian Federation (Group 3) To describe the safety profile of routine pediatric vaccines in healthy infants and toddlers in Mexico (Groups 1 and 2) and the Russian Federation (Groups 3 and 4)	
MET52	**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 Immunisation Schedule Having Meningococcal Group B Vaccine as Standard of Care** Phase III, open-label, randomised, parallel-group, active-controlled, multi-center study **Schedule:** Dose 1 at 3 months Dose 2 at 12 – 13 months **Control:** No meningococcal control vaccine **Concomitant vaccines:** Bexsero, Infanrix hexa, Rotarix, Prevnar 13 (PCV13)	Primary objective: To demonstrate the non-inferiority of the antibody responses to meningococcal serogroups A, C, W, and Y in terms of hSBA vaccine seroprotection (antibody titre ≥ 1:8) when MenACYW conjugate vaccine is administered concomitantly with Bexsero in the second year of life compared to when MenACYW conjugate vaccine is given alone. Secondary Objectives: 1) To compare the human complement serum bactericidal assay (hSBA) antibody response in terms of geometric mean titres (GMTs) against meningococcal serogroups A, C, W, and Y when MenACYW conjugate vaccine is administered concomitantly with Bexsero or when MenACYW conjugate vaccine is given alone in the second year of life 2) To describe the hSBA and rabbit complement serum bactericidal assay (rSBA) antibody responses against meningococcal serogroups A, C, W, and Y before and after the 1st dose of MenACYW conjugate vaccine administered at 3 months of age, before and after the 2nd dose of MenACYW conjugate vaccine administered at 12 to 13 months of age for Group 1 and Group 2 3) To describe the hSBA and rSBA antibody persistence against meningococcal serogroups A, C, W, and Y after the 1st dose of MenACYW conjugate vaccine administered at 3 months of age for Group 1 and Group 2 Safety Objectives: 4) To describe the safety of MenACYW conjugate vaccine when given alone and when administered concomitantly with Bexsero at 12 to 13 months of age 5) To describe the safety of Bexsero when given alone and when administered concomitantly with MenACYW conjugate vaccine at 12 to 13 months of age 6) To describe the safety of MenACYW conjugate vaccine when administered concomitantly with routine vaccines at 3 months of age	800 healthy infants aged ≥ 56 to ≤ 89 days (approximately 2 months of age) who were meningococcal, pneumococcal, diphtheria, tetanus, pertussis, hepatitis B, *Haemophilus influenzae* type b (Hib), poliovirus, and rotavirus vaccine-naïve in the UK **Study Groups: (**see 2.7.4 Addendum to Summary of Clinical Safety Group 1: MenACYW conjugate vaccine at 3 months and at 12 to 13 months of age; Bexsero at 2, 4, and 12 to 13 months of age Group 2: MenACYW conjugate vaccine at 3 months and at 12 to 13 months of age; Bexsero at 2 and 4 months of age Group 3: Bexsero at 2, 4, and 12 to 13 months of age Routine pediatric vaccines were to be given to individuals in all groups according to the UK immunisation schedule

Study Identifier/ Location of CSR	Study Title, Study Design, and Control	Objectives	Planned Sample Size / Population / Age at Enrollment / Study Groups
		7) To describe the safety of routine vaccines when given alone or administered concomitantly with MenACYW conjugate vaccine at 3 months of age 8) To describe the safety profile of routine vaccines and Bexsero administered concomitantly at 2 and 4 months of age	
MET41	**A Randomised Study to Describe the Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine Administered Concomitantly with Routine Pediatric Vaccines in Healthy Infants and Toddlers** Phase III, modified double-blind, randomised, parallel-group, active-controlled, multi-center study. **Schedule:** Dose 1 at 6 weeks-2 months Dose 2 at 4 months Dose 3 at 6 months Dose 4 at 12 – 15 months **Control:** Menveo **Concomitant vaccines:** DTaP, IPV, Hib, PCV13, Rotavirus, HB, MMR, V	Primary Objective: To describe the safety profile of MenACYW conjugate vaccine and Menveo when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers.	3080 healthy infants aged ≥ 42 to ≤ 89 days in the US and Puerto Rico **Study Groups: (**see 2.7.4 Addendum to Summary of Clinical Safety **Group 1**: MenACYW conjugate vaccine and routine pediatric vaccines at 2, 4, 6, and 12 months of age **Group 2**: Menveo and routine pediatric vaccines at 2, 4, 6, and 12 months of age
MET42	**Immunogenicity and Safety Study of an Investigational Quadrivalent Meningococcal Conjugate Vaccine when Administered Concomitantly with Routine Pediatric Vaccines in Healthy Infants and Toddlers** Phase III, modified double-blind, randomised, parallel-group, active-controlled, multi-center study. **Schedule:** Dose 1 at 6 weeks-2 months Dose 2 at 4 months Dose 3 at 6 months Dose 4 at 12 – 15 months **Control:** Menveo **Concomitant vaccines:** DTaP, IPV,	Primary Objectives: 1) To demonstrate the non-inferiority of hSBA vaccine seroresponse to meningococcal serogroups A, C, W, and Y following the administration of a 4 dose series of MenACYW conjugate vaccine compared to a 4 dose series of Menveo when given concomitantly with routine pediatric vaccines to infants and toddlers 6 weeks old to 15 months old. 2) To demonstrate the NI of the hSBA antibody response to meningococcal serogroups A, C, W, and Y following the administration of 3 doses in infancy of MenACYW conjugate vaccine compared to 3 doses in infancy of Menveo when given concomitantly with routine pediatric vaccines to infants at 2, 4, and 6 months of age. Secondary Objectives: 9) To demonstrate the non-inferiority of immune responses of the routine pediatric vaccines administered concomitantly with MenACYW conjugate vaccine as compared with Menveo in infants and toddlers 6 weeks old to 18 months old. 10) To assess the Ab responses against meningococcal serogroups A, C, W, and Y after the administration of the 4th dose of MenACYW conjugate vaccine or Menveo when both were given concomitantly with routine pediatric vaccines at 12 months of age.	2628 healthy infants aged ≥ 42 to ≤ 89 days in the US and Puerto Rico **Study Groups: (**see 2.7.4 Addendum to Summary of Clinical Safety **Group 1 (G1):** MenACYW conjugate vaccine and routine pediatric vaccines **Group 2 (G2):** Menveo and routine pediatric vaccines Each group was further randomised 2:1 in 2 subgroups based on the time of analyses conducted in the 2nd year of life (30 days after the 12-month vaccinations or 30 days after the 15-month vaccinations, respectively): **Group 1:** - Subgroup 1a (G1a) (12 months): MenACYW conjugate vaccine and routine pediatric vaccines at 2, 4, 6, and 12 to 15 months of age - Subgroup 1b (G1b) (15 months): MenACYW conjugate vaccine at 2, 4, 6, and 15 to 18 months of age and routine pediatric vaccines at 2, 4, 6, 12 to 15 months of age, and 15 to 18 months of age **Group 2:**

Study Identifier/ Location of CSR	Study Title, Study Design, and Control	Objectives	Planned Sample Size / Population / Age at Enrollment / Study Groups
	Hib, PCV13, Rotavirus, HB, MMR, V	11) To assess the persistence of bactericidal antibodies at 12 months of age in participants who previously received 3 doses of MenACYW conjugate vaccine or Menveo in infancy concomitantly with routine pediatric vaccines at 2, 4, and 6 months of age. 12) To describe the Ab responses against the antigens of the routine pediatric vaccines (Pentacel, PREVNAR 13, M-M-R II, VARIVAX, RotaTeq, and ENGERIX-B) when administered concomitantly with either MenACYW conjugate vaccine or Menveo. 13) To describe the Ab responses against meningococcal serogroups A, C, W, and Y when MenACYW conjugate vaccine versus (vs) Menveo was administered concomitantly with routine pediatric vaccines. 14) To describe the Ab responses against meningococcal serogroups A, C, W, and Y when MenACYW conjugate vaccine was administered to children 12 to 15 months of age vs when MenACYW conjugate vaccine was administered to children 15 to 18 months of age, concomitantly with routine pediatric vaccines (Subgroup 1a vs Subgroup 1b), including the bactericidal antibodies persistence and the effect of 4th dose of MenACYW conjugate vaccine at 12 to 15 months of age or 15 to 18 months of age. Safety: To describe the safety profile of MenACYW conjugate vaccine and Menveo when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers.	- Subgroup 2a (G2a) (12 months): Menveo at 2, 4, 6, and 12 months of age and routine pediatric vaccines at 2, 4, 6, 12, and 15 to 18 months of age - Subgroup 2b (G2b) (15 months): Menveo at 2, 4, 6, and 12 months of age and routine pediatric vaccines at 2, 4, 6, 12, and 15 to 18 months of age All participants received the recommended routine pediatric vaccines at the appropriate age.
MET61	**Immunogenicity And Safety Study Of An Investigational Quadrivalent Meningococcal Conjugate Vaccine Administered Concomitantly With Routine Pediatric Vaccines In Healthy Infants And Toddlers** Phase III, modified double-blind, randomised, parallel-group, active-controlled, multi-center study. **Schedule:** Dose 1 at 6 – 7 months (infants) Dose 2 at 12 – 13 months (older toddlers) **Control:** Control in infants: Menveo Control in older toddlers: Menactra **Concomitant vaccines:** DTaP, IPV, Hib, PCV13, Rotavirus, HB, MMR, V	Primary Objective: To demonstrate the non-inferiority of the vaccine seroresponse to meningococcal serogroups A, C, W, and Y following administration of 2 doses of MenACYW conjugate vaccine compared to 2 doses of Menveo when given concomitantly with routine pediatric vaccines to infants and toddlers at 6 to 7 months of age and 12 to 13 months of age. Secondary Objectives: 1) To demonstrate the non-inferiority of the percentage of participants with hSBA titres to meningococcal serogroups A, C, W, and Y ≥ 1:8 following administration of 2 doses of MenACYW conjugate vaccine compared to 2 doses of Menveo when given concomitantly with pediatric routine vaccines to infants and toddlers at 6 to 7 months of age and 12 to 13 months of age 2) To describe the antibody response against meningococcal serogroups A, C, W, and Y 30 days after the second vaccination at 12 to 13 months of age with MenACYW conjugate vaccine or Menveo 3) To describe the antibody response against meningococcal serogroups A, C, W, and Y 30 days after the first vaccination at 6 to 7 months of age with MenACYW conjugate vaccine or Menveo (in a subset of participants) 4) To describe the antibody response against meningococcal serogroups A, C, W, and Y 6 months after the first vaccination at 6 to 7 months of age with MenACYW conjugate vaccine or Menveo (in a subset of participants) 5) To describe the antibody response against meningococcal serogroups A, C, W, and Y 30 days after the second vaccination at 20 to 23 months of age with MenACYW conjugate vaccine or Menactra Safety: 1) To describe the safety profile of MenACYW conjugate vaccine and Menveo when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers	1070 healthy infants and toddlers: 870 healthy infants 6 to 7 months of age and 200 healthy toddlers 17 to 19 months of age in the US and Puerto Rico. **Study Groups: (**see 2.7.4 Addendum to Summary of Clinical Safety Group 1: MenACYW conjugate vaccine + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age Group 2: Menveo + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age Group 3: MenACYW conjugate vaccine at 17 to 19 months of age and 20 to 23 months of age Group 4: Menactra at 17 to 19 months of age and 20 to 23 months of age All participants in Group 1 and Group 2 were to receive a dose of either MenACYW conjugate vaccine or Menveo with the recommended pediatric vaccines at appropriate age.

Study Identifier/ Location of CSR	Study Title, Study Design, and Control	Objectives	Planned Sample Size / Population / Age at Enrollment / Study Groups
		2) To describe the safety profile of MenACYW conjugate vaccine and Menactra administered in toddlers	

Prevenar13: Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM197 Protein); M-M-RII : Measles, Mumps, and Rubella Virus Vaccine Live; Varivax: Varicella Virus Vaccine Live (Oka/Merck); Engerix-B**:** Hepatitis B vaccine; RotaTeq**:** Pentavalent rotavirus vaccine [RV5]); Havrix[i]: hepatitis A vaccine; Infanrix hexa: diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis (inactivated) and *Haemophilus influenzae* type b conjugate vaccine; Rotarix: human rotavirus vaccine; Synflorix: pneumococcal polysaccharide conjugate vaccine (PCV10); M-M-RVAXPRO: Measles, Mumps, and Rubella Virus Vaccine Live

2.3.2. Pharmacokinetics

No pharmacokinetics studies have been conducted. This is because pharmacokinetics studies are generally not needed for vaccines, consistent with current Guidelines on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1).

2.3.3. Pharmacodynamics

Pharmacodynamics of MenQuadfi vaccines represents the immune response to the vaccine. Since the efficacy of MenQuadfi vaccines is also assessed by immunological criteria, all clinical studies are discussed in the section 'Clinical efficacy'.

2.4. Clinical efficacy

All studies described in this section are immunogenicity studies, except study MET41. This is not addressed in this section as it investigated solely safety (as it investigated solely safety (see section 2.5 for further details).

Only study MET58 is considered as pivotal evidence for the current procedure to extend the indication to individuals aged 6 weeks to below 12 months. This is because among the provided studies, only study MET58 investigated comparison of MenQuadfi to Nimenrix (Meningococcal group A, C, W-135, and Y conjugate vaccine). Studies MET33, MET42, and MET61 applied MenACWY comparators that are not approved in the EU for the aforementioned population (Menveo, Menactra). These studies are addressed in the section 'Supportive studies'. Moreover, study MET52 had no MenACWY comparator but investigated concomitant vaccination with MenB vaccination (Bexsero) and is thus also addressed in the section 'Supportive studies'.

Menveo (Meningococcal (Groups A, C, Y and W 135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine) was used as comparator in studies MET33 (4-dose regimen, Group 2, starting at 2 months of age), MET42 (4-dose regimen, Group 2, starting at 2 months of age) and MET61 (2-dose regimen, Group 2, starting at 6 months of age). However, in the EU, Menveo is only authorised for administration to children starting from 2 years of age. In this regard, it is critically noted that in the procedure initially intended to extend the Menveo indication to children aged 2 - 23 months (Procedure no. EMEA/H/C/001095/II/0018), a positive risk balance in that population could not be established; this was also stated in the scientific advice given in 2023 (Case No.: EMA/SA/0000114629).

Menactra (Meningococcal (Serogroups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine) was administered with 2-dose regimen in Group 4 of Study MET61 in Group 4 in toddlers but is not approved in the EU (and in the US for children from 9 through 23 months of age, two doses, three months apart).

Studies MET33, MET42 and MET61 were subject of assessments in accordance with Article 46 of Regulation (EC) No 1901/2006 under procedures: EMEA/H/C/005084/P46/009, EMEA/H/C/005084/P46/013 and EMEA/H/C/005084/P46/012, respectively. Study MET52 was assessed via a type II variation pursuant to Article 16 of Commission Regulation (EC) No 1234/2008 under procedure: EMEA/H/C/007084/II/0027.

Different MenQuadfi dose regimens/vaccination schedules were investigated in the 5 immunogenicity studies:

- 3-dose (2+1 booster) regimen (studies MET58 and MET33),
- 2-dose (1+1 booster) regimen (studies MET52 and MET61)
- 4-dose (3+1 booster) regimen (Study MET42 and Group 4 of study MET58).

The MAH applied for a 3-dose (2+1) schedule for individuals starting meningococcal vaccination with 6 weeks of age and below 12 months of age.

2.4.1. Main study

Immunogenicity and Safety Study of a Quadrivalent Meningococcal Conjugate Vaccine When Co-administered With Routine Pediatric Vaccines in Healthy Infants and Toddlers in Europe

Methods

Study MET58 was a Phase 3, partially modified double-blind (open-label for some of the vaccines / study groups, as detailed below), randomised, parallel-group, active-controlled, multi-centre study to compare the immunogenicity and describe the safety of MenQuadfi (MenACYW conjugate vaccine) and Nimenrix (Meningococcal group A, C, W-135, and Y conjugate vaccine) when administered as a 3-dose series (i.e., 2 doses administered in infancy and 1 dose in the 2nd year of life) concomitantly with routine paediatric vaccines to healthy infants and toddlers in Europe.

Study design

Study MET58 was designed to demonstrate the non-inferiority (NI) of the antibody response against meningococcal serogroups A, C, W, and Y following the administration of a 3-dose series of MenACYW conjugate vaccine compared to a 3-dose series of Nimenrix when each vaccine was administered concomitantly with routine paediatric vaccines (PCV10 or PCV13 and hexavalent vaccine) to infants and toddlers from 6 weeks to 18 months old.

Approximately 1652 healthy infants aged 6 to 12 weeks of age (≥ 42 to ≤ 89 days) at enrolment were to be randomised as follows depending on the pneumococcal vaccines that was administered in the respective countries.

Countries where the pneumococcal vaccination administered was PCV10:

Subjects were to be randomised in a 1:1 ratio to 1 of the following 2 groups:

- Group 1: MenACYW conjugate vaccine (2+1 regimen) + PCV10 + Hexavalent vaccine +/- MMR vaccine
- Group 2: Nimenrix (2+1 regimen) + PCV10 + Hexavalent vaccine +/- MMR vaccine

Countries where the pneumococcal vaccination administered was PCV13:

220 subjects were to be randomised in a 1:1 ratio to one of the following 2 groups:

- Group 3: MenACYW conjugate vaccine (2+1 regimen) + PCV13 + Hexavalent vaccine +/- MMR vaccine
- Group 4: MenACYW conjugate vaccine (3+1 regimen) + PCV13 + Hexavalent vaccine +/- MMR vaccine

Table 1: Vaccination and blood sampling schedule in Groups 1, 2, and 3 – MET58

Visit # and age of individual	Visit 1 2 months		Visit 2 4 months	Visit 3 5 months	Visit 4 12 to 18 months		Visit 5* 13 to 19 months
Group	BL0001†	3 vaccinations	3 vaccinations	BL0002	BL0003†	4 vaccinations	BL0004
1	X	MenACYW conjugate vaccine Hexavalent vaccine‡ PCV10‡	MenACYW conjugate vaccine Hexavalent vaccine‡ PCV10‡	X	X	MenACYW conjugate vaccine Hexavalent vaccine‡ PCV10‡ MMR vaccine	X
2	X	Nimenrix Hexavalent vaccine‡ PCV10‡	Nimenrix Hexavalent vaccine‡ PCV10‡	X	X	Nimenrix Hexavalent vaccine‡ PCV10‡ MMR vaccine	X
3	X	MenACYW conjugate vaccine Hexavalent vaccine‡ PCV13‡	MenACYW conjugate vaccine Hexavalent vaccine‡ PCV13‡	X	X	MenACYW conjugate vaccine Hexavalent vaccine‡ PCV13‡ MMR vaccine	X

PCV10: Synflorix
PCV13: Prevenar 13
MMR vaccine (M-M-RVAXPRO®) could be received concomitantly with other vaccines at Visit 4.
*Last study visit for Groups 1, 2, and 3. Other routine vaccines could be administered as per standard of care after study procedures were completed.
†Blood was drawn prior to vaccinations.
‡The hexavalent vaccine and PCV10 (or PCV13 in Group 3) were administered as a 2+1 regimen, concomitantly with the 1st and 2nd doses in infancy and the toddler dose of MenACYW conjugate vaccine. Individuals in Finland, Sweden or Poland should have received the licensed rotavirus vaccine concomitantly with study vaccines at Visit 1 and Visit 2. No serological testing was done for rotavirus immunogenicity.

Table 2: Vaccination and blood sampling schedule in Group 4 – MET58

Visit # and age of individual	Visit 1 2 months		Visit 2 4 months	Visit 3 6 months	Visit 4 7 months	Visit 5 12 to 18 months		Visit 6* 13 to 19 months
Group	BL0001†	3 vaccinations	3 vaccinations	1 vaccination	BL0002	BL0003†	4 vaccinations	BL0004
4	X	MenACYW conjugate vaccine Hexavalent vaccine‡ PCV13‡	MenACYW conjugate vaccine Hexavalent vaccine PCV13	MenACYW conjugate vaccine§	X	X	MenACYW conjugate vaccine Hexavalent vaccine PCV13 MMR vaccine	X

PCV13: Prevenar 13®
MMR vaccine (M-M-RVAXPRO) should have received concomitantly with other vaccines at Visit 5.
*Last study visit for Group 4. Other routine vaccines should be administered as per standard of care after study procedures were completed.
†Blood was drawn prior to vaccinations.
‡The hexavalent vaccine and Prevenar 13 were administered as a 2+1 regimen, concomitantly with the 1st and 2nd doses in infancy and the toddler dose of MenACYW conjugate vaccine.
§The 3rd dose of MenACYW conjugate vaccine was administered alone, without any other routine pediatric vaccines.

Study participants

As per Protocol version 7.0, dated 03 February 2022:

Inclusion Criteria

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

1. Aged ≥42 to ≤89 days on the day of the first study visit
2. Healthy infants as determined by medical history, physical examination and judgment of the Investigator
3. Informed consent form has been signed and dated by the parent(s) or other legally acceptable representative
4. Subject and parent/legally acceptable representative are able to attend all scheduled visits and to comply with all study procedures
5. Covered by health insurance according to local regulations

Exclusion Criteria

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

1. Participation at the time of study enrolment (or in the 4 weeks preceding the first study vaccination) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure.
2. Receipt of any vaccine in the 4 weeks preceding the first study vaccination or planned receipt of any vaccine in the 4 weeks before and/or following any study vaccination except for influenza vaccination and rotavirus vaccination, which may be received at a gap of at least 2 weeks before or 2 weeks after any study vaccines. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines. This exclusion criterion does not apply to subjects in Finland, Sweden or Poland who plan to receive the licensed rotavirus vaccine concomitantly with study vaccines at study vaccination visits V1 and V2.
3. Receipt or planned receipt during the study period vaccination against meningococcal disease with either the study vaccine or another vaccine (i.e., mono- or polyvalent, polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C, W, or Y; or meningococcal B serogroup-containing vaccine
4. Previous vaccination against diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b (Hib), poliovirus, *Streptococcus pneumoniae*, measles, mumps, or rubella. Previous vaccination against hepatitis B specific to risk groups, as per local recommendation
5. Receipt of immune globulins, blood or blood-derived products since birth
6. Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy; or long term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks) since birth
7. Family history of congenital or hereditary immunodeficiency, unless the immune competence of the potential vaccine recipient is demonstrated
8. Individuals with blood dyscrasias, leukaemia, lymphoma of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems
9. Individuals with active tuberculosis
10. History of Neisseria meningitidis infection, confirmed either clinically, serologically, or microbiologically
11. History of diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, measles, mumps, rubella, and of *Haemophilus influenzae* type b, and / or *Streptococcus pneumoniae* infection or disease

12. At high risk for meningococcal infection during the study (specifically, but not limited to, subjects with persistent complement deficiency, with anatomic or functional asplenia, or subjects traveling to countries with high endemic or epidemic disease)
13. Individuals with underlying conditions predisposing them to invasive pneumococcal disease (specifically, but not limited to, subjects with sickle cell disease or human immunodeficiency virus [HIV] infection)
14. History of any neurologic disorders, including seizures and progressive neurologic disorders
15. History of Guillain-Barré syndrome
16. Known systemic hypersensitivity to any of the vaccine components, or history of a severe allergic reaction (e.g., anaphylaxis) to the vaccine(s) used in the study or to a vaccine containing any of the same substances including neomycin, streptomycin, polymyxin B, glutaraldehyde, formaldehyde, and gelatine
17. Verbal report of thrombocytopenia, contraindicating intramuscular vaccination in the investigator's opinion
18. Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination in the investigator's opinion
19. Chronic illness (including, but not limited to, cardiac disorders, congenital heart disease, chronic lung disease, renal disorders, auto-immune disorders, diabetes, psychomotor diseases, and known congenital or genetic diseases) that, in the opinion of the investigator, is at a stage where it might interfere with study conduct or completion
20. Any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives
21. Moderate or severe acute illness/infection (according to investigator judgment) on the day of vaccination or febrile illness (temperature ≥38.0°C). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided.
22. Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw
23. Identified as a natural or adopted child of the Investigator or employee with direct involvement in the proposed study
24. Infants born preterm (by less than 37 weeks of gestation) requiring specific immunisation schedule for routine childhood vaccines and/or specific care at the time of vaccination, as per national recommendations

Treatments

Studied vaccine and comparator:

- MenQuadfi, MenACYW conjugate vaccine: Meningococcal Polysaccharide (Serogroups A, C, W, and Y) Tetanus Toxoid Conjugate Vaccine
- Nimenrix: Meningococcal group A, C, W-135, and Y conjugate vaccine.

Identity of other products (concomitant vaccines):

- Hexavalent vaccine, DTaP-IPV-HB-Hib: Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and *Haemophilus influenzae* type b conjugate vaccine (adsorbed) (authorised products: Hexyon, Hexacima)
- PCV10, Synflorix: Pneumococcal polysaccharide conjugate vaccine (adsorbed)
- PCV13, Prevenar 13: Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)
- MMR vaccine, M-M-RVAXPRO: Measles, mumps, and rubella vaccine (live)

Objectives

Primary Objective

- To demonstrate the non-inferiority (NI) of the antibody response against meningococcal serogroups A, C, W, and Y following the administration of a 3-dose series of MenACYW conjugate vaccine compared to a 3-dose series of Nimenrix when each vaccine was administered concomitantly with routine paediatric vaccines (pneumococcal conjugate vaccine 10-valent, absorbed [PCV10] and hexavalent vaccine) to infants and toddlers from 6 weeks to 18 months of age (Group 1 versus Group 2)

NI was demonstrated if all 4 individual null hypotheses (4 serogroups) were rejected. For each serogroup, the 2-sided 95% CI of the GMT ratio Group 1 (MenACYW) / Group 2 (Nimenrix) had to lie above 1/1.5.

Secondary Objectives

1. To demonstrate the NI of the antibody response against meningococcal serogroups A, C, W, and Y following the administration of 2 doses in infancy of MenACYW conjugate vaccine compared to 2 doses in infancy of Nimenrix when each vaccine was administered concomitantly with routine paediatric vaccines (PCV10 and hexavalent vaccine) (Group 1 versus Group 2)
2. To describe the antibody responses against meningococcal serogroups A, C, W, and Y when MenACYW conjugate vaccine was administered in a 3-dose series concomitantly with the routine paediatric vaccines (Group 3)
3. To describe the antibody responses against the antigens of the routine paediatric vaccines administered in a 3-dose series concomitantly with MenACYW conjugate vaccine or Nimenrix (Groups 1, 2, and 3)
4. To describe the antibody responses against meningococcal serogroups A, C, W, and Y measured by serum bactericidal assay using human complement (hSBA) when MenACYW conjugate vaccine or Nimenrix was administered in a 3-dose series concomitantly with PCV10 and other routine paediatric vaccines (Groups 1 and 2)
5. To describe the antibody responses against meningococcal serogroups A, C, W, and Y measured by hSBA when MenACYW conjugate vaccine was administered in a 4-dose series concomitantly with pneumococcal conjugate vaccine (13-valent, absorbed) (PCV13) and other routine paediatric vaccines (Group 4)
6. To describe the antibody responses against the antigens of the routine paediatric vaccines administered concomitantly with MenACYW conjugate vaccine administered in a 4-dose series (Group 4)

Observational Objectives

Immunogenicity

- To describe the antibody responses against meningococcal serogroups A, C, W, and Y measured by serum bactericidal assay using baby rabbit complement (rSBA) in a subset of subjects when MenACYW conjugate vaccine or Nimenrix was administered concomitantly with routine paediatric vaccines (all groups)

Safety

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

Outcomes/endpoints

Primary Endpoint

- Antibody titres (geometric mean titres [GMTs]) against meningococcal serogroups A, C, W, and Y measured by hSBA in Groups 1 and 2, 30 days after the booster dose (3rd dose/toddler dose) of MenACYW conjugate vaccine or Nimenrix when administered concomitantly with routine paediatric vaccines (PCV10 and hexavalent vaccine) to infants and toddlers from 6 weeks to 18 months of age (Group 1 versus Group 2)

Secondary Endpoints

1. Antibody titres ≥ 1:8 against meningococcal serogroups A, C, W, and Y assessed at 30 days after dose 2 of MenACYW conjugate vaccine or Nimenrix measured by hSBA, when administered concomitantly with routine paediatric vaccines (Group 1 versus Group 2)
2. Antibody titres (GMTs) against meningococcal serogroups A, C, W, and Y measured by hSBA in Group 3 at the following time points:
    - Day (D) 0 (before dose 1 of MenACYW conjugate vaccine)

    In addition, the following endpoints were assessed:

    - Antibody titres ≥ 1:4 and titres ≥ 1:8
    - 30 days after Dose 2 of MenACYW conjugate vaccine in infancy, and before and 30 days after the booster dose (dose 3)

    In addition, the following endpoints were assessed:

    - Antibody titres ≥ 1:4 and titres ≥ 1:8
    - Post-vaccination titres ≥ 4 times the latest pre vaccination titres
    - hSBA vaccine seroresponse for serogroups A, C, W, and Y was defined as:
        - For a subject with a pre vaccination titre < 1:8, the post-vaccination titre had to be ≥ 1:16
        - For a subject with a pre vaccination titre ≥ 1:8, the post-vaccination titre had to be at least 4-fold greater than the pre vaccination titre
3. Antibody titres or concentrations against the antigens of hexavalent vaccine (diphtheria, tetanus, and acellular pertussis [DTaP]-inactivated polio vaccine [IPV]-hepatitis b [HB]-*Haemophilus influenzae* type b [Hib]) in Groups 1, 2, and 3 at the following time points:

- D0 (before dose 1)
  - Anti-pertussis antibody concentrations (pertussis toxin [PT], filamentous hemagglutinin [FHA])
- 30 days after dose 2 in infancy
  - Antibody concentrations/titres for all antigens
  - Anti-tetanus antibody concentrations ≥ 0.01 international units (IU) / milliliter (mL), ≥ 0.1 IU/mL and ≥ 1.0 IU/mL
  - Anti-diphtheria antibody concentrations ≥ 0.01 IU/mL, ≥ 0.1 IU/mL, ≥ 1.0 IU/mL
  - Anti-poliovirus types 1, 2, and 3 antibody titres ≥ 1:8
  - Anti-polyribosyl-ribitol phosphate (PRP) antibody concentrations ≥ 0.15 µg/mL and ≥ 1.0 µg/mL
  - Pertussis vaccine seroresponse for anti-PT and anti-FHA, defined as:
    - If the pre-primary vaccination concentration is < 4 × lower level of quantification (LLOQ), post-primary vaccination concentration ≥ 4 × LLOQ
    - If the pre-primary vaccination concentration is ≥ 4 × LLOQ, post-primary vaccination concentration ≥ pre-primary vaccination concentration
  - Anti-hepatitis B surface antigen (HBsAg) antibody concentrations ≥ 10 mIU/mL and ≥ 100 mIU/mL
- Before and 30 days after the booster dose (dose 3):
  - Antibody concentrations/titres for all antigens
  - Anti-tetanus antibody concentrations ≥ 0.01 IU/mL, ≥ 0.1 IU/mL and ≥ 1.0 IU/mL
  - Anti-diphtheria antibody concentrations ≥ 0.01 IU/mL, ≥ 0.1 IU/mL and ≥ 1.0 IU/mL
  - Anti-poliovirus types 1, 2, and 3 antibody titres ≥ 1:8
  - Anti-PRP antibody concentrations ≥ 0.15 µg/mL and ≥ 1.0 µg/mL
  - Pertussis vaccine seroresponse for anti-PT and anti-FHA, defined as:
    - If the pre-booster vaccination concentration is < 4 × LLOQ, post-booster vaccination concentration ≥ 4 × pre-booster concentration
    - If the pre-booster vaccination concentration is ≥ 4 × LLOQ, post-booster vaccination concentration ≥ 2 × pre-booster concentration
  - Anti-HBsAg antibody concentrations ≥ 10 mIU/mL and ≥ 100 mIU/mL

Antibody concentrations against the antigens of PCV10 in Groups 1 and 2, 30 days after dose 2 in infancy and 30 days after the booster dose (dose 3):

- Anti-pneumococcal antibody concentrations for serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F
- Anti-pneumococcal antibody concentrations ≥ 0.35 µg/mL and ≥ 1.0 µg/mL for serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F

Antibody concentrations against the antigens of PCV13 in Group 3, 30 days after dose 2 in infancy and 30 days after the booster dose (dose 3):

- Anti-pneumococcal antibody concentrations for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F
- Anti-pneumococcal antibody concentrations ≥ 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

Antibody concentrations against the antigens of measles, mumps, and rubella (MMR) vaccine 30 days after the MMR vaccine injection (When the MMR vaccine had been administered concomitantly with the study vaccines)

- Antibody concentrations for all antigens
- Anti-measles antibody concentrations (serostatus cutoff: 255 mIU/mL)
- Anti-mumps antibody concentrations (serostatus cutoff: 10 Mumps Ab units/mL)
- Anti-rubella antibody concentrations (serostatus cutoff: 10 IU/mL)

4. Antibody titres against meningococcal serogroups A, C, W, and Y measured by hSBA in Groups 1 and 2, as detailed for the Secondary Endpoints 2 (similar time points and endpoints)
5. Antibody titres (GMTs) against meningococcal serogroups A, C, W, and Y measured by hSBA in Group 4 on Day 0 (before dose 1 of MenACYW conjugate vaccine), 30 days after dose 3 in infancy, and before and 30 days after the booster dose (dose 4) at the following timepoints:
   - D0 (before dose 1 of MenACYW conjugate vaccine)

   In addition, the following endpoints were assessed:

   - Antibody titres ≥ 1:4 and titres ≥ 1:8
   - 30 days after dose 3 of MenACYW conjugate vaccine in infancy, and before and 30 days after the booster dose (Dose 4)

   In addition, the following endpoints were assessed:

   - Antibody titres ≥ 1:4 and titres ≥ 1:8
   - Post-vaccination titres ≥ 4 times the latest pre vaccination titres
   - hSBA vaccine seroresponse for serogroups A, C, W, and Y was defined as:
     - For a subject with a pre vaccination titre < 1:8, the post-vaccination titre had to be ≥ 1:16;
     - For a subject with a pre vaccination titre ≥ 1:8, the post-vaccination titre had to be at least 4-fold greater than the pre vaccination titre.
6. For Group 4, antibody titres or concentrations against the antigens of DTaP-IPV-HB-Hib vaccine before and 30 days after the booster dose (dose 4), antibody concentrations against the antigens of PCV13 vaccine 30 days after the booster dose (dose 4), and antibody concentrations against the antigens of MMR vaccine 30 days after vaccination (When the MMR vaccine had been administered concomitantly with the study vaccines).

   The timepoints were:

Antibody titres or concentrations against the antigens of hexavalent vaccine (DTaP-IPV-HB-Hib):

- Pre-booster dose and at 30 days after the booster dose (dose 4):

  Antibody concentrations/titres for all antigens

  - Anti-tetanus antibody concentrations ≥ 0.01 IU/mL, ≥ 0.1 IU/mL, and ≥ 1.0 IU/mL
  - Anti-diphtheria antibody concentrations ≥ 0.01 IU/mL, ≥ 0.1 IU/mL, and ≥ 1.0 IU/mL
  - Anti-poliovirus types 1, 2, and 3 antibody titres ≥ 1:8
  - Anti-PRP antibody concentrations ≥ 0.15 µg/mL and ≥ 1.0 µg/mL
  - Anti-pertussis antibody concentration and pertussis vaccine seroresponse for anti-PT and anti-FHA, defined as:
    - If the pre-booster vaccination concentration was < 4 × LLOQ, post-booster vaccination concentration ≥ 4 × pre-booster concentration
    - If the pre-booster vaccination concentration was ≥ 4 × LLOQ, post-booster vaccination concentration ≥ 2 × pre-booster concentration

Anti-HBsAg antibody concentrations ≥ 10 mIU/mL and ≥ 100 mIU/mL

Antibody concentrations against the antigens of PCV13 in Group 4, 30 days after the booster dose (dose 4):

- Anti-pneumococcal antibody concentrations for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F
- Anti-pneumococcal antibody concentrations ≥ 0.35 µg/mL for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F

Antibody concentrations against the antigens of MMR vaccine 30 days after the MMR vaccine injection (When the MMR vaccine had been administered concomitantly with the study vaccines)

- Antibody concentrations for all antigens
- Anti-measles antibody concentrations (serostatus cutoff: 255 mIU/mL)
- Anti-mumps antibody concentrations (serostatus cutoff: 10 mumps Ab units/mL)
- Anti-rubella antibody concentrations (serostatus cutoff: 10 IU/mL)

Observational Endpoints

Immunogenicity Endpoints

- Antibody titres (GMTs) against meningococcal serogroups A, C, W, and Y measured by rSBA in a subset of subjects in all groups (The rSBA subset comprised: Group 1 and Group 2: 100 subjects in each group and Group 3 and Group 4: 50 subjects in each group) at Day 0 (before Dose 1) (all groups), 30 days after dose 2 (Groups 1, 2, and 3) or 30 days after dose 3 (Group 4) in infancy, and before and 30 days after the booster dose (in all groups)

In addition, the following endpoints were assessed for all groups:

- Antibody titres, titres ≥ 1:8, and titres ≥ 1:128

- Post-vaccination titres ≥ 4 times the latest pre vaccination titres
- rSBA vaccine seroresponse for serogroups A, C, W, and Y is defined as:
  - a post-vaccination rSBA titre ≥ 1:32 for subjects with pre-vaccination rSBA titre < 1:8, or
  - a post-vaccination titre ≥ 4 times the pre vaccination titre for subjects with pre-vaccination rSBA titre ≥ 1:8.

Safety Endpoints

For safety, it is referred to the section on clinical safety.

Threshold definitions for immunogenicity endpoints:

hSBA vaccine seroprotection is defined as: hSBA titres ≥ 1:8.

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

- For an individual with a pre vaccination titre < 1:8, the post-vaccination titre had to be ≥ 1:16

For an individual with a pre vaccination titre ≥ 1:8, the post-vaccination titre had to be at least 4-fold greater than the pre vaccination titre

Sample size

Protocol version 7.0, dated 03 February 2022:

With 716 enrolled subjects in Group 1 and in Group 2, the study will have 96.2% power to declare the non-inferiority of Group 1 versus Group 2 based on A, C, W, Y hSBA antibody titres (ratio of GMTs in the 2 groups) after a 3-dose series to infants and toddlers 6 weeks to 18 months old, assuming:

An estimated 26.2% dropout rate from the PPAS (528 subjects evaluable by group), a 1-sided alpha level of 2.5%, a non-inferiority margin of 1.5 (GMT ratio), standard deviation (SD) of log10-transformed titres of 0.7 for serogroups A and C, 0.5 for serogroup Y, and 0.6 for serogroup W. SDs are based on the results of the MET39 (NCT01049035) MenACYW 2/4/12 months schedule (Group 3) after booster results. For the power computation, the same SD in the control group (Nimenrix) is assumed.

Randomisation

Protocol version 7.0, dated 03 February 2022:

On the day of enrolment, subjects who meet the inclusion/exclusion criteria and whose parent / legally acceptable representative sign the ICF will be randomly assigned to Groups 1 through 4. [In] Countries where PCV10 will be administered for pneumococcal vaccination, 1432 subjects will be randomised in a 1:1 ratio to 2 groups such that Groups 1 and 2 will have approximately 716 subjects each; and countries where PCV13 will be administered for pneumococcal vaccination, 220 subjects will be randomised in a 1:1 ratio to 2 groups such Groups 3 and 4 will have approximately 110 subjects each.

Randomisation will be performed with permuted block method with stratification by centre and age categories as follows: approximately 6 to 8 weeks (≥ 42 to ≤ 59 days), and 9 to 12 weeks (≥ 60 to ≤ 89 days).

Blinding (masking)

MET58 was a partially modified double-blind study (open label for some vaccines / study groups [double-blind for Group 1 and Group 2 and open label for Group 3 and Group 4]).

Protocol version 7.0, dated 03 February 2022:

To perform an appropriate description of the safety of MenACYW conjugate vaccine and Nimenrix in Groups 1 and 2 (i.e., when each of these vaccines is administered as a 3-dose series concomitantly with PCV10 and hexavalent vaccine), MenACYW conjugate vaccine and Nimenrix will be administered in a modified double-blind manner in these 2 groups. The MenACYW conjugate vaccine in Groups 3 and 4 and all other concomitant vaccines in all vaccine groups will be administered in an open-label manner.

A modified double-blind trial means that the subject's parent / legally acceptable representative, the Investigator, and other study personnel remain unaware of the treatment assignments throughout the trial. An unblinded vaccine administrator will administer the appropriate vaccine but will not be involved in safety data collection.

Given that the meningococcal vaccines in Groups 3 and 4 have different vaccination schedules in the number of vaccines administered and timing of their administration, these vaccines will be administered in an open-label manner.

Other concomitant vaccines in all groups will be administered in an open-label manner to ensure the subjects received appropriate vaccines as per local standard of care.

Statistical methods

Protocol version 7.0, dated 03 February 2022:

Primary hypotheses (co-primary)

Assuming that Log10 transformation of the data follows a normal distribution, the Log10(data) will be used for the statistical analysis, then antilog transformations will be applied to the results of calculations, in order to provide the results in terms of GMT. The statistical methodology will be based on the use of the 2-sided 95% confidence interval (CI) of the ratio of post-vaccination GMTs between Group 1 and Group 2. The CI will be calculated using a normal approximation of log-transformed titres. Non-inferiority will be demonstrated if all 4 individual null hypotheses (4 serogroups) are rejected. For each serogroup, the 2-sided 95% CI of the GMT ratio Group 1 (MenACYW) / Group 2 (Nimenrix) should lie above 1/1.5.

Secondary hypotheses (co-primary)

Non-inferiority will be demonstrated if all 4 individual null hypotheses (4 serogroups) are rejected. If the lower limit of the 2-sided 95% CI of the difference between the 2 percentages is > -10%, the non-inferiority will be demonstrated. The CI of the difference in percentages will be computed using the Wilson score method without continuity correction.

The statistical analyses for the Secondary Objectives 2, 3, 4, 5, 6 and 7 will be descriptive.

Analysis sets

The main immunogenicity analyses will be performed on the PPAS analysis set including PPAS2 for the primary objective and PPAS1 for secondary objective 1, and will be confirmed on the FAS2 and FAS1. In the FAS1 and FAS2, subjects will be analyzed by the vaccine group to which they were randomised.

Per-Protocol Analysis Set for Primary Series (PPAS1)

The subjects presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS1:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not complete the vaccination schedule
- Subject received a vaccine other than the one that he / she was randomised to receive
- Preparation and / or administration of vaccine was not done as per-protocol
- Subject did not receive vaccine in the proper time window
    - Visit 2: Visit 1 + 60 days (+14 days)
    - Visit 3 (Group 4 only): Visit 2 + 60 days (+14 days)
- Subject did not provide a post-dose serology sample in the proper time window or a post-dose serology sample was not drawn
    - Blood sampling 2 (BL0002):
        - Visit 3: Visit 2 + 30 days [+21 days] (Group 1, 2, 3)
        - Visit 4: Visit 3 + 30 days [+21 days] (Group 4)
- Subject received a protocol-prohibited therapy / medication / vaccine (identified among category 2 / category 3, not including the rotavirus vaccine administered at V1 and V2)
- Subject had other protocol violations that affected the subject's immune response, as determined by the clinical team before locking the database

In addition to the reasons listed above, subjects will also be excluded from the PPAS1 if their serology sample did not produce a valid test result (i.e., results for all antigens are missing).

Vaccine correctness criteria apply to all the vaccines administered in the protocol, (i.e., MenACYW conjugate vaccine / Nimenrix and the concomitants vaccines.

In the event of a local or national immunisation program with a pandemic influenza or coronavirus vaccine or any other vaccine as needed, subjects who receive the 1 or more doses of a pandemic influenza or coronavirus vaccine at any time during the study will not be withdrawn from the study.

Per-Protocol Analysis Set for Booster Series (PPAS2)

The subjects presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS2:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not complete the vaccination schedule
- Subject received a vaccine other than the one that he / she was randomised to receive
- Preparation and / or administration of vaccine was not done as per-protocol
- Subject did not receive vaccine in the proper time window for the booster dose at 12 to 18 months of age (all groups) or at least 180 days after Visit 3 (Group 4)

- Subject did not provide a post-dose serology sample in the proper time window or a post-dose serology sample was not drawn
    - Blood sampling 4 (BL0004):
        - Visit 5: Visit 4 + 30 days [+21 days] (Group 1, 2, 3)
        - Visit 6: Visit 5 + 30 days [+21 days] (Group 4)
- Subject received a protocol-prohibited therapy / medication / vaccine (identified among category 2 / category 3)
- Subject had other protocol violations that affected the subject's immune response, as determined by the clinical team before locking the database

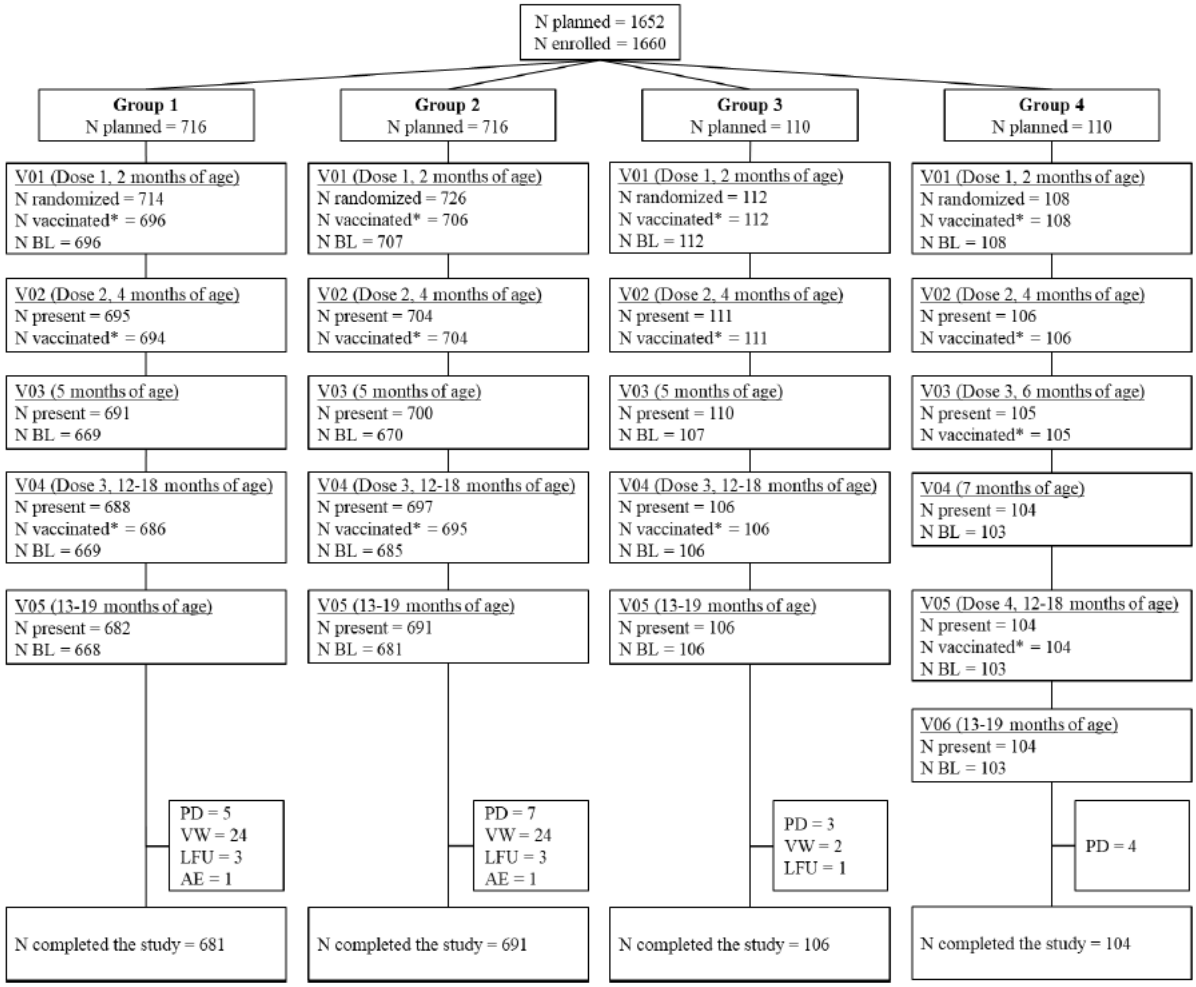
In addition to the reasons listed above, subjects will also be excluded from the PPAS2 if their serology sample did not produce a valid test result (i.e., results for all antigens are missing).

Vaccine correctness criteria apply to all the vaccines administered in the protocol, i.e., MenACYW conjugate vaccine / Nimenrix and the concomitant vaccines. A licensed Measles, Mumps and Rubella vaccine must be received either during the study visit (Visit 4/Visit 5) or with a gap of at least 4 weeks before any study vaccines or after the end of the study. In the event of a local or national immunisation program with a pandemic influenza or coronavirus vaccine or any other vaccine as needed, subjects who receive the 1 or more doses of a pandemic influenza or coronavirus vaccine at any time during the study will not be withdrawn from the study.

Results

Participant flow

Table 3: Subject disposition flow chart



AE, adverse event; BL, blood sample; LFU, lost to follow-up; PD, protocol deviation; V, visit; VW, voluntary withdrawal by parent(s)/LAR(s)l
*The numbers of subjects who received MenACYW conjugate vaccine (Groups 1, 3, and 4) or Nimenrix (Group 2) are presented.

Visit 1 (at 6 to 12 weeks of age, all groups)

The 1st dose of MenACYW conjugate vaccine had been administered to 696 subjects (97.5%) in Group 1, 112 subjects (100%) in Group 3, and 108 subjects (100%) in Group 4.

The 1st dose of Nimenrix had been administered to 706 subjects (97.2%) in Group 2.

A total of 696 subjects (97.5%) in Group 1, 707 subjects (97.4%) in Group 2, 112 subjects (100%) in Group 3, and 108 subjects (100%) in Group 4 received the hexavalent vaccine.

A total of 696 subjects (97.5%) in Group 1 and 707 subjects (97.4%) in Group 2 received Synflorix.

A total of 112 subjects (100%) in Group 3, and 108 subjects (100%) in Group 4 received Prevenar 13.

There were 696 subjects (97.5%) in Group 1, 707 subjects (97.4%) in Group 2, 112 subjects (100%) in Group 3, 108 subjects (100%) in Group 4 who provided a blood sample.

A total of 18 subjects in Group 1 and 20 subjects in Group 2 did not receive MenACYW conjugate vaccine and Nimenrix, respectively. The main reason was withdrawal by parent(s)/LAR(s). A total of 18

subjects in Group 1 and 19 subjects in Group 2, did not provide a blood sample. All subjects in Groups 3 and 4 provided a blood sample.

Visit 2 (at 4 months of age, all groups)

A total of 695 subjects (97.3%) in Group 1, 704 subjects (97.0%) in Group 2, 111 subjects (99.1%) in Group 3, and 106 subjects (98.1%) in Group 4 were present.

The 2nd dose of MenACYW conjugate vaccine had been administered to 694 subjects (97.2%) in Group 1, 111 subjects (99.1%) in Group 3, and 106 subjects (98.1%) in Group 4.

The 2nd dose of Nimenrix had been administered to 704 subjects (97.0%) in Group 2.

A total of 695 subjects (97.3%) in Group 1, 704 subjects (97.0%) in Group 2, 110 subjects (98.2%) in Group 3, and 106 subjects (98.1%) in Group 4 received the hexavalent vaccine.

A total of 695 subjects (97.3%) in Group 1 and 704 subjects (97.0%) in Group 2 received Synflorix.

A total of 110 subjects (98.2%) in Group 3, and 106 subjects (98.1%) in Group 4 received Prevenar 13.

No blood sampling was planned at this visit.

Visit 3 (at 5 months of age, Groups 1, 2, and 3)

A total of 691 subjects (96.8%) in Group 1, 700 subjects (96.4%) in Group 2, and 110 subjects (98.2%) in Group 3 were present.

There were 669 subjects (93.7%) in Group 1, 670 subjects (92.3%) in Group 2, and 107 subjects (95.5%) in Group 3 who provided a blood sample.

A total of 22 subjects in Group 1, 30 subjects in Group 2, and 3 subjects in Group 3 did not provide a blood sample.

Visit 3 (at 6 months of age, Group 4)

In Group 4, 105 subjects (97.2%) were present, and all received the 3rd dose of MenACYW conjugate vaccine.

No blood sample was planned at this visit.

Visit 4 (at 12-18 months of age, Groups 1, 2, and 3)

A total of 688 subjects (96.4%) in Group 1, 697 subjects (96.0%) in Group 2, and 106 (94.6%) in Group 3 were present.

The 3rd dose of MenACYW conjugate vaccine had been administered to 686 subjects (96.1%) in Group 1 and 106 subjects (94.6%) in Group 3.

The 3rd dose of Nimenrix had been administered to 695 subjects (95.7%) in Group 2.

A total of 684 subjects (95.8%) in Group 1, 694 subjects (95.6%) in Group 2, and 105 subjects (93.8%) in Group 3 received the hexavalent vaccine.

A total of 684 subjects (95.8%) in Group 1 and 694 subjects (95.6%) in Group 2 received Synflorix.

A total of 105 subjects (93.8%) in Group 3 received Prevenar 13.

A total of 669 subjects (93.7%) in Group 1, 685 subjects (94.4%) in Group 2, and 106 subjects (94.6%) in Group 3 provided a blood sample.

A total of 2 subjects in Group 1 and 2 subjects in Group 2 did not receive MenACYW conjugate vaccine and Nimenrix, respectively.

A total of 19 subjects in Group 1 and 12 subjects in Group 2 did not provide a blood sample. All subjects in Group 3 provided a blood sample.

Visit 4 (at 7 months of age, Group 4)

A total of 104 subjects (96.3%) in Group 4 were present and 103 subjects (95.4%) provided a blood sample.

One subject did not provide a blood sample at this visit.

Visit 5 (at 13-19 months of age, Groups 1, 2, and 3)

A total of 682 subjects (95.5%) in Group 1, 691 subjects (95.2%) in Group 2, and 106 subjects (94.6%) in Group 3 were present.

There were 668 subjects (93.6%) in Group 1, 681 subjects (93.8%) in Group 2, and 106 subjects (94.6%) in Group 3 who provided a blood sample.

A total of 14 subjects in Group 1 and 10 subjects in Group 2 did not provide a blood sample. All subjects in Group 3 provided a blood sample.

Visit 5 (at 12-18 months of age, Group 4)

A total of 104 subjects (96.3%) in Group 4 were present and all received the 4th dose of MenACYW conjugate vaccine.

A total of 101 subjects (93.5%) in Group 4 received the hexavalent vaccine and Prevenar 13.

There were 103 subjects (95.4%) in Group 4 who provided a blood sample.

One subject in Group 4 did not provide a blood sample at this visit.

During the study, the main reason for non-vaccination with MenACYW conjugate vaccine or Nimenrix was withdrawal by parent(s)/LAR(s).

A total of 681 subjects (95.4%) in Group 1, 691 subjects (95.2%) in Group 2, 106 subjects (94.6%) in Group 3, and 104 subjects (96.3%) in Group 4 completed the study.

The reasons for early termination in Group 1 were:

- withdrawal by parent(s)/LAR(s) (24 subjects)
- protocol deviation (5 subjects)
- lost to follow-up (3 subjects)
- AE (1 subject with poor weight gain at Visit 2 assessed as not related to study vaccine)

The reasons for early termination in Group 2 were:

- withdrawal by parent(s)/LAR(s) (24 subjects)
- protocol deviation (7 subjects)
- lost to follow-up (3 subjects)
- AE (1 subject with a food allergy that led to study withdrawal at Visit 4 and assessed as not related to study vaccine)

The reasons for early termination in Group 3 were:

- protocol deviation (3 subjects)
- withdrawal by parent(s)/LAR(s) (2 subjects)

- lost to follow-up (1 subject)

The reason for early termination in Group 4 was withdrawal by parent(s)/LAR(s) (4 subjects).

Less than 10% of subjects were impacted by the COVID-19 pandemic situation.

Table 4: Disposition by randomised group for Group 1, Group 2, and Group 3 - All Randomised Subjects

Age/Dose #	Visit Timepoint		Group 1 (N=714) n (%)	Group 2 (N=726) n (%)	Group 3 (N=112) n (%)	All (N=1552) n (%)
2 Months (Dose 1)	V01	Randomized	714 (100)	726 (100)	112 (100)	1552 (100)
		BL performed	696 (97.5)	707 (97.4)	112 (100)	1515 (97.6)
		Injected MenACYW	696 (97.5)	0	112 (100)	808 (52.1)
		Injected Nimenrix	0	706 (97.2)	0	706 (45.5)
		Injected DTaP-IPV-HB-Hib	696 (97.5)	707 (97.4)	112 (100)	1515 (97.6)
		Injected Prevenar 13	0	0	112 (100)	112 (7.2)
		Injected Synflorix	696 (97.5)	707 (97.4)	0	1403 (90.4)
4 Months (Dose 2)	V02	Present	695 (97.3)	704 (97.0)	111 (99.1)	1510 (97.3)
		Injected MenACYW	694 (97.2)	0	111 (99.1)	805 (51.9)
		Injected Nimenrix	0	704 (97.0)	0	704 (45.4)
		Injected DTaP-IPV-HB-Hib	695 (97.3)	704 (97.0)	110 (98.2)	1509 (97.2)
		Injected Prevenar 13	0	0	110 (98.2)	110 (7.1)
		Injected Synflorix	695 (97.3)	704 (97.0)	0	1399 (90.1)
5 Months	V03	Present	691 (96.8)	700 (96.4)	110 (98.2)	1501 (96.7)
		BL performed	669 (93.7)	670 (92.3)	107 (95.5)	1446 (93.2)
12-18 Months (Dose 3)	V04	Present	688 (96.4)	697 (96.0)	106 (94.6)	1491 (96.1)
		BL performed	669 (93.7)	685 (94.4)	106 (94.6)	1460 (94.1)
		Injected MenACYW	686 (96.1)	0	106 (94.6)	792 (51.0)
		Injected Nimenrix	1 (0.1)	695 (95.7)	0	696 (44.8)
		Injected DTaP-IPV-HB-Hib	684 (95.8)	694 (95.6)	105 (93.8)	1483 (95.6)
		Injected Prevenar 13	0	0	105 (93.8)	105 (6.8)
		Injected Synflorix	684 (95.8)	694 (95.6)	0	1378 (88.8)
		Injected M-M-RVAXPRO	648 (90.8)	658 (90.6)	105 (93.8)	1411 (90.9)
13-19 Months	V05	Present	682 (95.5)	691 (95.2)	106 (94.6)	1479 (95.3)
		BL performed	668 (93.6)	681 (93.8)	106 (94.6)	1455 (93.8)

n: number of subjects fulfilling the item listed
N: total number of subjects randomized in each study group
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix ® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 3: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.
Study: MET58 Program: t08014.sas Datasets=ADSL ADEX ADIS Output: PRODOPS/SP0047/MET58/CSR_01/REPORT/OUTPUT/T08014_i.rtf (26AUG2024 11:33)
Source: Section 8, Table 8.14

Table 5: Disposition by randomised group for Group 4 - All Randomised Subjects

Age/Dose #	Visit Timepoint		Group 4 (N=108) n (%)
2 Months (Dose 1)	V01	Randomized	108 (100)
		BL performed	108 (100)
		Injected MenACYW	108 (100)
		Injected DTaP-IPV-HB-Hib	108 (100)
		Injected Prevenar 13	108 (100)
4 Months (Dose 2)	V02	Present	106 (98.1)
		Injected MenACYW	106 (98.1)
		Injected DTaP-IPV-HB-Hib	106 (98.1)
		Injected Prevenar 13	106 (98.1)
6 Months (Dose 3)	V03	Present	105 (97.2)
		Injected MenACYW	105 (97.2)
7 Months	V04	Present	104 (96.3)
		BL performed	103 (95.4)
12-18 Months (Dose 4)	V05	Present	104 (96.3)
		BL performed	103 (95.4)
		Injected MenACYW	104 (96.3)
		Injected DTaP-IPV-HB-Hib	101 (93.5)
		Injected Prevenar 13	101 (93.5)
		Injected M-M-RVAXPRO	104 (96.3)
13-19 Months	V06	Present	104 (96.3)
		BL performed	103 (95.4)

n: number of subjects fulfilling the item listed
N: total number of subjects randomized in each study group
Group 4: MenACYW conjugate vaccine administered at 2, 4, 6 and 12 to 18 months of age. Routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.
Study: MET58 Program: t08015.sas Datasets=ADSL ADEX ADIS Output: PRODOPS/SP0047/MET58/CSR_01/REPORT/OUTPUT/T08015_i.rtf (26AUG2024 11:32)
Source: Section 8. Table 8.15

Protocol deviations

Table 6: Major and critical protocol deviations by randomised group - Randomised Study Subjects

	Group 1 (N=714) n (%)	Group 2 (N=726) n (%)	Group 3 (N=112) n (%)	Group 4 (N=108) n (%)	All (N=1660) n (%)
Study participants with at least one major or critical protocol deviation	332 (46.5)	333 (45.9)	38 (33.9)	40 (37.0)	743 (44.8)
Study participants with at least one major protocol deviation	332 (46.5)	333 (45.9)	38 (33.9)	40 (37.0)	743 (44.8)
Informed consent not obtained for an amendment requiring a reconsent	13 (1.8)	11 (1.5)	4 (3.6)	9 (8.3)	37 (2.2)
Informed consent obtained with an error in consent process or documentation	5 (0.7)	13 (1.8)	1 (0.9)	0	19 (1.1)
Born at full term of pregnancy (>= 37 weeks) and with a birth weight >= 2.5 kg	0	1 (0.1)	0	1 (0.9)	2 (0.1)
Healthy infants as determined by medical history, physical examination and judgment of the Investigator	0	1 (0.1)	0	1 (0.9)	2 (0.1)
Subject and parent/legally acceptable representative are not able to attend all scheduled visits and to comply with all study procedures	0	1 (0.1)	0	0	1 (<0.1)
Previous vaccination against diphtheria, tetanus, pertussis, Haemophilus influenzae type b (Hib), poliovirus, Streptococcus pneumoniae, measles, mumps, or rubella. Previous vaccination against..	0	1 (0.1)	0	0	1 (<0.1)
Receipt of immune globulins, blood or blood-derived products since birth	3 (0.4)	0	1 (0.9)	0	4 (0.2)
Any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives	2 (0.3)	1 (0.1)	0	0	3 (0.2)
Infants born preterm (by less than 37 weeks of gestation) requiring specific immunization schedule for routine childhood vaccines and/or specific care at the time of vaccination, as per national ..	0	1 (0.1)	0	0	1 (<0.1)
Protocol-specified co-administered routine vaccine not received	29 (4.1)	33 (4.5)	6 (5.4)	4 (3.7)	72 (4.3)
Protocol specified co-administered routine vaccine was administered but not within the protocol-specified time window	66 (9.2)	57 (7.9)	4 (3.6)	9 (8.3)	136 (8.2)
Protocol prohibited therapy/medication/vaccine received	98 (13.7)	105 (14.5)	8 (7.1)	2 (1.9)	213 (12.8)
Protocol-specified co-administered routine vaccine was administered but not as per protocol..	0	3 (0.4)	0	0	3 (0.2)
Subject received an unacceptable protocol specified co-administered routine vaccine for use	1 (0.1)	0	0	0	1 (<0.1)
Protocol specified co-administered routine vaccine administered while under a protocol-specified definite contraindication	0	0	1 (0.9)	0	1 (<0.1)
Study visit, telephone call or safety contact was not performed	26 (3.6)	34 (4.7)	5 (4.5)	5 (4.6)	70 (4.2)
Study visit, telephone call or safety contact was not performed within the protocol-specified time window	67 (9.4)	53 (7.3)	15 (13.4)	23 (21.3)	158 (9.5)
Planned sample not performed	71 (9.9)	77 (10.6)	6 (5.4)	5 (4.6)	159 (9.6)
Planned sample not performed within the protocol-specified time window	67 (9.4)	64 (8.8)	4 (3.6)	1 (0.9)	136 (8.2)
Study procedure performed by unqualified / unauthorized personnel	0	1 (0.1)	0	0	1 (<0.1)
Sample handled incorrectly during collection, processing, storage or shipment	16 (2.2)	15 (2.1)	3 (2.7)	0	34 (2.0)
IMP was not administered	27 (3.8)	30 (4.1)	6 (5.4)	4 (3.7)	67 (4.0)
IMP was administered but not within the protocol-specified time window	61 (8.5)	54 (7.4)	2 (1.8)	8 (7.4)	125 (7.5)
Subject/ patient received an unacceptable IMP for use	4 (0.6)	1 (0.1)	1 (0.9)	3 (2.8)	9 (0.5)
IMP given outside randomization procedure	1 (0.1)	0	0	0	1 (<0.1)
Randomization procedure not performed in the correct sequence as specified in the protocol	3 (0.4)	7 (1.0)	0	0	10 (0.6)
Subject randomized twice	1 (0.1)	3 (0.4)	1 (0.9)	0	5 (0.3)
IMP number actually given to the subject is different from the IMP number allocated by the randomization process	2 (0.3)	3 (0.4)	3 (2.7)	1 (0.9)	9 (0.5)
Failure to report AE/AESI/SAE to sponsor within the protocol-specified time window (ex 24h for SAE and AESI)	4 (0.6)	5 (0.7)	2 (1.8)	0	11 (0.7)
Failure to complete AE/AESI/SAE when information is available	2 (0.3)	1 (0.1)	0	0	3 (0.2)
30 minutes or immediate reaction post follow up not completed	1 (0.1)	0	0	0	1 (<0.1)
Missing or not provided subject's diary card	26 (3.6)	20 (2.8)	8 (7.1)	6 (5.6)	60 (3.6)
Inexistent, missing or incomplete source data	1 (0.1)	0	0	1 (0.9)	2 (0.1)
Privacy authorization not obtained	1 (0.1)	2 (0.3)	0	0	3 (0.2)
Other	36 (5.0)	34 (4.7)	0	0	70 (4.2)
Concomitant Vaccines (protocol specified co-administered routine vaccines) number actually given to the subject is different from the Concomitant Vaccines number allocated by the randomization process	0	1 (0.1)	0	0	1 (<0.1)
Study participants with at least one critical protocol deviation	0	0	0	0	0

n: number of subjects fulfilling the item listed
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix ® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 3: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.
Group 4: MenACYW conjugate vaccine administered at 2, 4, 6 and 12 to 18 months of age. Routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.
Study: MET58 Program: t08013.sas Datasets=ADSL ADDV Output: PRODOPS/SP0047/MET58/CSR_01/REPORT/OUTPUT/T08013_i.rtf (26AUG2024 11:32)
Source: Section 8, Table 8.13

Recruitment

Study initiation date: 14 December 2018 (first subject first visit)

Study completion: last subject last visit: 17 May 2023

Database lock date: 08 July 2024.

This study was conducted at 33 centres that enrolled and randomised subjects in 7 countries: Czech Republic, Finland, Italy, Spain, Sweden, Poland, and Romania.

Conduct of the study

Protocol	7.0	2022-02-03	Finalized after first subject in - previous versions not available
	2.0	2018-07-09	Would be the last version before first subject in
SAP	1.0	2024-04-24	Before last subject last visit

Baseline data

Table 7: Baseline demographics by randomised group - All Randomised Subjects

	Group 1 (N=714)	Group 2 (N=726)	Group 3 (N=112)	Group 4 (N=108)	All (N=1660)
Sex: n (%)					
Male	359 (50.3)	348 (47.9)	67 (59.8)	50 (46.3)	824 (49.6)
Female	355 (49.7)	378 (52.1)	45 (40.2)	58 (53.7)	836 (50.4)
Sex ratio: Male/Female	1.01	0.92	1.49	0.86	0.99
Age: (Days)					
M	714	726	112	108	1660
Mean (SD)	72.6 (12.2)	72.4 (12.1)	62.5 (7.12)	63.3 (7.93)	71.2 (12.1)
Min ; Max	42.0 ; 89.0	42.0 ; 89.0	43.0 ; 84.0	43.0 ; 86.0	42.0 ; 89.0
Median	76.0	75.5	63.0	63.5	73.0
Q1 ; Q3	64.0 ; 83.0	65.0 ; 82.0	59.0 ; 65.5	59.5 ; 67.0	63.0 ; 81.0
Age group: n (%)					
>= 42 to <= 59 days	114 (16.0)	115 (15.8)	29 (25.9)	27 (25.0)	285 (17.2)
>= 60 to 89 days	600 (84.0)	611 (84.2)	83 (74.1)	81 (75.0)	1375 (82.8)
Racial origin: n (%)					
American Indian or Alaska Native	0	0	1 (0.9)	0	1 (<0.1)
Asian	2 (0.3)	1 (0.1)	4 (3.6)	2 (1.9)	9 (0.5)
Black or African American	0	0	1 (0.9)	3 (2.8)	4 (0.2)
Native Hawaiian or Other Pacific Islander	0	1 (0.1)	0	0	1 (<0.1)
White	693 (97.1)	699 (96.3)	106 (94.6)	101 (93.5)	1599 (96.3)
Not Reported	13 (1.8)	16 (2.2)	0	1 (0.9)	30 (1.8)
Unknown	2 (0.3)	3 (0.4)	0	0	5 (0.3)
Multiple origin	4 (0.6)	6 (0.8)	0	1 (0.9)	11 (0.7)
Ethnicity: n (%)					
Hispanic or Latino	17 (2.4)	12 (1.7)	77 (68.8)	75 (69.4)	181 (10.9)
Not Hispanic or Latino	642 (89.9)	660 (90.9)	35 (31.3)	33 (30.6)	1370 (82.5)
Not Reported	51 (7.1)	52 (7.2)	0	0	103 (6.2)
Unknown	4 (0.6)	2 (0.3)	0	0	6 (0.4)
Gestational age: n (%)					
Preterm birth	15 (2.1)	14 (1.9)	0	0	29 (1.7)
Full-term birth	698 (97.8)	710 (97.8)	112 (100)	108 (100)	1628 (98.1)
Missing	1 (0.1)	2 (0.3)	0	0	3 (0.2)

n: number of subjects fulfilling the item listed in the first column. M: number of subjects with available data for the relevant endpoint.
N: number of subjects randomized in each study group
Q1; Q3: first quartile; third quartile. SD: standard deviation.
Preterm infant born at gestational age <37 weeks; full-term infant born at gestational age >=37 weeks.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix ® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 3: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.
Group 4: MenACYW conjugate vaccine administered at 2, 4, 6 and 12 to 18 months of age. Routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.
Study: MET58 Program: t08019to26.sas Dataset=ADSL Output: PRODOPS/SP0047/MET58/CSR_01/REPORT/OUTPUT/T08019_i.rtf (12SEP2024 11:31)
Source: Section 8, Table 8.19

Numbers analysed

Table 8: Immunogenicity analysis sets by randomised group for primary series - All Randomised Subjects

	Group 1 (N=714) n (%)	Group 2 (N=726) n (%)	Group 3 (N=112) n (%)	Group 4 (N=108) n (%)	All (N=1660) n (%)
Full Analysis Set 1	669 (93.7)	670 (92.3)	107 (95.5)	102 (94.4)	1548 (93.3)
Did not receive at least 1 dose of the study vaccine in the primary series	18 (2.5)	19 (2.6)	0	0	37 (2.2)
Did not have a valid post-primary series vaccination blood sample result	45 (6.3)	56 (7.7)	5 (4.5)	6 (5.6)	112 (6.7)
Per Protocol Analysis Set 1	522 (73.1)	524 (72.2)	96 (85.7)	90 (83.3)	1232 (74.2)
Subjects with at least one deviation	192 (26.9)	202 (27.8)	16 (14.3)	18 (16.7)	428 (25.8)
Did not meet all protocol-specified inclusion/exclusion criteria	5 (0.7)	5 (0.7)	1 (0.9)	1 (0.9)	12 (0.7)
Did not complete the vaccinations schedule for primary series	19 (2.7)	22 (3.0)	2 (1.8)	3 (2.8)	46 (2.8)
Received vaccine other than randomized or at least one unknown received vaccine	1 (0.1)	1 (0.1)	0	0	2 (0.1)
Vaccine not prepared/administered as per-protocol	1 (0.1)	1 (0.1)	1 (0.9)	0	3 (0.2)
Did not receive vaccine in time window	55 (7.7)	47 (6.5)	2 (1.8)	7 (6.5)	111 (6.7)
Did not provide a post-dose serology sample or not in the proper time window	68 (9.5)	78 (10.7)	9 (8.0)	8 (7.4)	163 (9.8)
Received protocol-prohibited therapy/medication/vaccine	84 (11.8)	89 (12.3)	5 (4.5)	1 (0.9)	179 (10.8)
Did not provide a valid blood test result	0	0	0	1 (0.9)	1 (<0.1)
Other protocol deviations	0	0	0	0	0

n: number of subjects fulfilling the item listed
N: total number of subjects randomized in each study group
Note: A subject may be associated with more than 1 deviation.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix ® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 3: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.
Group 4: MenACYW conjugate vaccine administered at 2, 4, 6 and 12 to 18 months of age. Routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.
Study: MET58 Program: t08016.sas Dataset=ADSL Output: PRODOPS/SP0047/MET58/CSR_01/REPORT/OUTPUT/T08016_i.rtf (26AUG2024 11:32)
Source: Section 8, Table 8.16

Table 9: Immunogenicity analysis sets by randomised group for booster series - All Randomised Subjects

	Group 1 (N=714) n (%)	Group 2 (N=726) n (%)	Group 3 (N=112) n (%)	Group 4 (N=108) n (%)	All (N=1660) n (%)
Full Analysis Set 2	668 (93.6)	680 (93.7)	106 (94.6)	102 (94.4)	1556 (93.7)
Did not receive at least 1 dose of the study vaccine at booster vaccination	27 (3.8)	30 (4.1)	6 (5.4)	4 (3.7)	67 (4.0)
Did not have a valid post-booster vaccination blood sample result	46 (6.4)	46 (6.3)	6 (5.4)	6 (5.6)	104 (6.3)
Per Protocol Analysis Set 2	560 (78.4)	584 (80.4)	94 (83.9)	90 (83.3)	1328 (80.0)
Subjects with at least one deviation	154 (21.6)	142 (19.6)	18 (16.1)	18 (16.7)	332 (20.0)
Did not meet all protocol-specified inclusion/exclusion criteria	5 (0.7)	5 (0.7)	1 (0.9)	1 (0.9)	12 (0.7)
Did not complete the vaccinations schedule	30 (4.2)	33 (4.5)	8 (7.1)	7 (6.5)	78 (4.7)
Received vaccine other than randomized or at least one unknown received vaccine	2 (0.3)	1 (0.1)	0	0	3 (0.2)
Vaccine not prepared/administered as per-protocol	5 (0.7)	2 (0.3)	1 (0.9)	0	8 (0.5)
Did not receive vaccine in time window	13 (1.8)	7 (1.0)	2 (1.8)	1 (0.9)	23 (1.4)
Did not provide a post-dose serology sample or not in the proper time window	91 (12.7)	89 (12.3)	13 (11.6)	12 (11.1)	205 (12.3)
Received protocol-prohibited therapy/medication/vaccine	14 (2.0)	18 (2.5)	2 (1.8)	0	34 (2.0)
Did not provide a valid blood test result	0	1 (0.1)	0	1 (0.9)	2 (0.1)
Other protocol deviations	36 (5.0)	34 (4.7)	0	0	70 (4.2)

n: number of subjects fulfilling the item listed
N: total number of subjects randomized in each study group
Note: A subject may be associated with more than 1 deviation.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix ® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 3: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.
Group 4: MenACYW conjugate vaccine administered at 2, 4, 6 and 12 to 18 months of age. Routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.
Study: MET58 Program: t08017.sas Dataset=ADSL Output: PRODOPS/SP0047/MET58/CSR_01/REPORT/OUTPUT/T08017_i.rtf (26AUG2024 11:32)
Source: Section 8, Table 8.17

Outcomes and estimation

Primary Immunogenicity Objective: Non-inferiority of hSBA Antibody Response After 3-dose Series of MenACYW Conjugate Vaccine Versus Nimenrix (Groups 1 and 2)

Table 10: Non-inferiority of hSBA vaccine antibody titres at D30 after the 12 to 18-month vaccination for Group 1 versus 2 - Per-Protocol Analysis Set 2

	Group 1 (N=560)			Group 2 (N=584)			Group 1/Group 2		
Serogroup	M	GMT	95% CI	M	GMT	95% CI	Ratio	95% CI	Non-inferiority
A	543	131	(113 ; 151)	567	189	(165 ; 218)	0.690	(0.565 ; 0.842)	No
C	550	565	(505 ; 632)	578	120	(106 ; 135)	4.73	(4.00 ; 5.58)	Yes
Y	554	285	(260 ; 313)	579	160	(145 ; 177)	1.78	(1.55 ; 2.04)	Yes
W	547	423	(382 ; 468)	575	275	(247 ; 305)	1.54	(1.33 ; 1.78)	Yes

M: Number of subjects with available data for the endpoint
N: number of subjects in per-protocol analysis set 2, for booster series
95% CI of the GM calculated on Log10 titers using the usual calculation for normal distribution, then antilog transformations will be applied to the results of calculations.
95% CI of the ratio calculated using a normal approximation of log-transformed titers.
The non-inferiority will be demonstrated if the lower limit of the 2-sided 95% CI is > 1/1.5 for all four serogroups.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix ® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.

Secondary Objective #1: Non-Inferiority of hSBA Antibody Response Post-Dose 2 of MenACYW Conjugate Vaccine Versus Nimenrix (Groups 1 and 2)

Table 11: Non-inferiority of the percentage of subjects with hSBA antibody titres >=1:8 at D30 after the 4-month vaccination for Group 1 versus 2 - Per-Protocol Analysis Set 1

	Group 1 (N=522)			Group 2 (N=524)			Group 1 - Group 2		
Serogroup	n/M	%	95% CI	n/M	%	95% CI	Difference (%)	95% CI	Non-inferiority
A	323/508	63.6	(59.2 ; 67.8)	385/508	75.8	(71.8 ; 79.5)	-12.20	(-17.74 ; -6.56)	No
C	507/513	98.8	(97.5 ; 99.6)	479/521	91.9	(89.3 ; 94.1)	6.89	(4.44 ; 9.62)	Yes
Y	498/516	96.5	(94.5 ; 97.9)	489/523	93.5	(91.0 ; 95.5)	3.01	(0.34 ; 5.77)	Yes
W	500/518	96.5	(94.6 ; 97.9)	494/523	94.5	(92.1 ; 96.3)	2.07	(-0.49 ; 4.70)	Yes

n: Number of subjects with hSBA antibody titers that met the criterion.
M: Number of subjects with available data for the endpoint.
N: number of subjects in per-protocol analysis set 1, for primary series.
95% CI of the single proportion calculated from the exact binomial method.
95% CI of the difference calculated from the Wilson Score method without continuity correction.
The overall non-inferiority will be demonstrated if the lower limit of the 2-sided 95% CI is > -10% for all four serogroups.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix ® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.

Secondary Objective #2: Antibody Responses Against Meningococcal A, C, Y, and W Serogroups After a 3-dose Series of MenACYW Conjugate Vaccine (Group 3)

hSBA Antibody GMTs (Group 3)

Table 12: Summary of geometric means of hSBA titres at D0 before the 2-month vaccination and at D30 after the 4-month vaccination for Group 3 - Per-Protocol Analysis Set 1

			Group 3 (N=96)	
Serogroup	Time Point	M	GMT	95% CI
A	D0 before dose 1	94	3.00	(2.58 ; 3.49)
	D30 after dose 2	91	14.8	(10.6 ; 20.8)
C	D0 before dose 1	94	3.91	(3.16 ; 4.84)
	D30 after dose 2	95	309	(235 ; 407)
Y	D0 before dose 1	94	2.85	(2.45 ; 3.32)
	D30 after dose 2	96	73.4	(57.7 ; 93.5)
W	D0 before dose 1	94	2.67	(2.40 ; 2.96)
	D30 after dose 2	96	102	(79.7 ; 131)

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, for primary series.
95% CI calculated using calculation for normal distribution on log10(titer) following by antilog transformation.
Group 3: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

Table 13: Summary of geometric means of hSBA titres at D0 before and at D30 after the 12 to 18-month vaccination for Group 3 - Per-Protocol Analysis Set 2

Serogroup	Time Point	M	Group 3 (N=94) GMT	95% CI
A	D0 before booster dose (Dose 3)	91	5.18	(4.22 ; 6.37)
	D30 after booster dose (Dose 3)	92	104	(67.9 ; 161)
C	D0 before booster dose (Dose 3)	94	26.2	(18.7 ; 36.8)
	D30 after booster dose (Dose 3)	93	819	(622 ; 1078)
Y	D0 before booster dose (Dose 3)	94	33.0	(25.0 ; 43.5)
	D30 after booster dose (Dose 3)	94	589	(470 ; 737)
W	D0 before booster dose (Dose 3)	93	39.1	(29.6 ; 51.8)
	D30 after booster dose (Dose 3)	87	1049	(782 ; 1406)

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, for booster series.
95% CI calculated using calculation for normal distribution on log10(titer) following by antilog transformation.
Group 3: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

hSBA Antibody Titres >= 1:4 and >= 1:8 (Group 3)

Table 14: Percentage of subjects with hSBA titre >= 1:4 and >= 1:8 at D0 before the 2-month vaccination and at D30 after the 4-month vaccination for Group 3 - Per-Protocol Analysis Set 1

Serogroup	Time Point	hSBA Titers	n/M	Group 3 (N=96) %	95% CI
A	D0 before dose 1	>=1:4	31/94	33.0	(23.6 ; 43.4)
		>=1:8	14/94	14.9	(8.4 ; 23.7)
	D30 after dose 2	>=1:4	72/91	79.1	(69.3 ; 86.9)
		>=1:8	58/91	63.7	(53.0 ; 73.6)
C	D0 before dose 1	>=1:4	41/94	43.6	(33.4 ; 54.2)
		>=1:8	25/94	26.6	(18.0 ; 36.7)
	D30 after dose 2	>=1:4	94/95	98.9	(94.3 ; 100)
		>=1:8	94/95	98.9	(94.3 ; 100)
Y	D0 before dose 1	>=1:4	25/94	26.6	(18.0 ; 36.7)
		>=1:8	12/94	12.8	(6.8 ; 21.2)
	D30 after dose 2	>=1:4	95/96	99.0	(94.3 ; 100)
		>=1:8	92/96	95.8	(89.7 ; 98.9)
W	D0 before dose 1	>=1:4	27/94	28.7	(19.9 ; 39.0)
		>=1:8	10/94	10.6	(5.2 ; 18.7)
	D30 after dose 2	>=1:4	95/96	99.0	(94.3 ; 100)
		>=1:8	93/96	96.9	(91.1 ; 99.4)

n: number of subjects experiencing the endpoint listed in the first 3 columns.
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, for primary series.
95% CI of the single proportion calculated from the exact binomial method.
Group 3: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

Table 15: Percentage of subjects with hSBA titre >= 1:4 and >= 1:8 at D0 before and at D30 after the 12 to 18-month vaccination for Group 3 - Per-Protocol Analysis Set 2

Serogroup	Time Point	hSBA Titers	n/M	Group 3 (N=94) %	95% CI
A	D0 before booster dose (Dose 3)	>=1:4	60/91	65.9	(55.3 ; 75.5)
		>=1:8	34/91	37.4	(27.4 ; 48.1)
	D30 after booster dose (Dose 3)	>=1:4	85/92	92.4	(84.9 ; 96.9)
		>=1:8	82/92	89.1	(80.9 ; 94.7)
C	D0 before booster dose (Dose 3)	>=1:4	82/94	87.2	(78.8 ; 93.2)
		>=1:8	75/94	79.8	(70.2 ; 87.4)
	D30 after booster dose (Dose 3)	>=1:4	93/93	100	(96.1 ; 100)
		>=1:8	93/93	100	(96.1 ; 100)
Y	D0 before booster dose (Dose 3)	>=1:4	89/94	94.7	(88.0 ; 98.3)
		>=1:8	84/94	89.4	(81.3 ; 94.8)
	D30 after booster dose (Dose 3)	>=1:4	94/94	100	(96.2 ; 100)
		>=1:8	94/94	100	(96.2 ; 100)
W	D0 before booster dose (Dose 3)	>=1:4	90/93	96.8	(90.9 ; 99.3)
		>=1:8	86/93	92.5	(85.1 ; 96.9)
	D30 after booster dose (Dose 3)	>=1:4	87/87	100	(95.8 ; 100)
		>=1:8	87/87	100	(95.8 ; 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 serogroup and time point
N: number of subjects in per-protocol analysis set 2, for booster series.
95% CI of the single proportion calculated from the exact binomial method.
Group 3: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

Table 16: Distribution of hSBA titres at D0 before and at D30 after the 12 to 18-month vaccination for Group 3 - Per-Protocol Analysis Set 2

Serogroup	Time Point	hSBA Titers	n/M	%
A	D0 before booster dose (Dose 3)	<1:4	31/91	34.1
		>=1:4	60/91	65.9
		>=1:8	34/91	37.4
		>=1:16	18/91	19.8
		>=1:32	8/91	8.8
		>=1:64	4/91	4.4
		>=1:128	1/91	1.1
	D30 after booster dose (Dose 3)	<1:4	7/92	7.6
		>=1:4	85/92	92.4
		>=1:8	82/92	89.1
		>=1:16	74/92	80.4
		>=1:32	70/92	76.1
		>=1:64	59/92	64.1
		>=1:128	52/92	56.5
		>=1:256	45/92	48.9
		>=1:512	34/92	37.0
		>=1:1024	19/92	20.7
		>=1:2048	3/92	3.3
		>=1:4096	1/92	1.1
		>=1:8192	1/92	1.1
C	D0 before booster dose (Dose 3)	<1:4	12/94	12.8

n: number of subjects experiencing the endpoint listed in the first 3 columns
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, for booster series.
Percentages are based on M.
Group 3: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

hSBA Antibody Titres >= 4-Fold Rise Increase (Group 3)

Table 17: Number and percentage of subjects with >= 4-fold rise of hSBA titre from pre-2-month vaccination to D30 after the 4-month vaccination for Group 3 - Per-Protocol Analysis Set 1

Serogroup	n/M	Group 3 (N=96) %	95% CI
A	51/89	57.3	(46.4 ; 67.7)
C	86/93	92.5	(85.1 ; 96.9)
Y	87/94	92.6	(85.3 ; 97.0)
W	91/94	96.8	(91.0 ; 99.3)

n: number of subjects with valid serology results for the particular serogroup and who met the criterion.
M: number of subjects with valid serology results for the particular serogroup.
N: number of subjects in per-protocol analysis set 1, for primary series.
Percentages are based on M.
95% CI of the single proportion calculated from the exact binomial method.
Group 3: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

Table 18: Number and percentage of subjects with >= 4-fold rise of hSBA titre from pre-2-month vaccination to D30 after the 12 to 18-month vaccination for Group 3 - Per-Protocol Analysis Set 2

Serogroup	n/M	Group 3 (N=94) %	95% CI
A	74/90	82.2	(72.7 ; 89.5)
C	91/91	100	(96.0 ; 100)
Y	92/92	100	(96.1 ; 100)
W	85/85	100	(95.8 ; 100)

n: number of subjects with valid serology results for the particular serogroup and who met the criterion.
M: number of subjects with valid serology results for the particular serogroup and time period.
N: number of subjects in per-protocol analysis set 2, for booster series.
Percentages are based on M.
95% CI of the single proportion calculated from the exact binomial method.
Group 3: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

hSBA Seroresponse (Group 3)

Table 19: Summary of hSBA vaccine seroresponse rate at D30 after the 4-month vaccination for Group 3 - Per-Protocol Analysis Set 1

Serogroup	n/M	Group 3 (N=96) %	95% CI
A	46/89	51.7	(40.8 ; 62.4)
C	86/93	92.5	(85.1 ; 96.9)
Y	84/94	89.4	(81.3 ; 94.8)
W	89/94	94.7	(88.0 ; 98.3)

n: Number of subjects who achieve the hSBA vaccine seroresponse.
M: number of subjects with valid serology results for the particular serogroup.
N: number of subjects in per-protocol analysis set 1, for primary series.
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.
95% CI of the single proportion calculated from the exact binomial method.
Group 3: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

Table 20: Summary of hSBA vaccine seroresponse rate at D30 after the 12 to 18-month vaccination compared to D0 before the 2-month vaccination for Group 3 - Per-Protocol Analysis Set 2

		Group 3 (N=94)	
Serogroup	n/M	%	95% CI
A	69/90	76.7	(66.6 ; 84.9)
C	90/91	98.9	(94.0 ; 100)
Y	92/92	100	(96.1 ; 100)
W	85/85	100	(95.8 ; 100)

n: Number of subjects who achieve the hSBA vaccine seroresponse.
M: number of subjects with valid serology results for the particular serogroup and time period.
N: number of subjects in per-protocol analysis set 2, for booster series.
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.
95% CI of the single proportion calculated from the exact binomial method.
Group 3: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

Secondary Objective #3: Antibody Responses Against the Antigens of the Concomitant Routine Vaccines After a 3-dose Series of MenACYW Conjugate Vaccine Versus Nimenrix (Groups 1, 2, and 3)

Anti-pertussis antibody concentration (PT and FHA)

Table 21: Summary of geometric means of anti-pertussis antibodies at D0 before the 2-month vaccination for Groups 1 to 3 - Per-Protocol Analysis Set 1

		Group 1 (N=522)			Group 2 (N=524)			Group 3 (N=96)	
Antigens	M	GMC	95% CI	M	GMC	95% CI	M	GMC	95% CI
Anti-PT	520	2.97	(2.68 ; 3.29)	521	2.61	(2.38 ; 2.87)	95	11.0	(8.74 ; 14.0)
Anti-FHA	520	10.8	(9.73 ; 12.1)	521	10.1	(9.10 ; 11.2)	95	55.6	(42.4 ; 73.0)

M: Number of subjects with available data for the endpoint.
N: number of subjects in per-protocol analysis set 1, for primary series.
95% CI calculated using calculation for normal distribution on log10(titer) following by antilog transformation.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 3: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

Table 22: Summary of Pertussis vaccine seroresponse rate for anti-PT and anti-FHA at D30 after the 4-month vaccination for Groups 1 to 3 - Per-Protocol Analysis Set 1

		Group 1 (N=522)			Group 2 (N=524)			Group 3 (N=96)	
Antigens	n/M	%	95% CI	n/M	%	95% CI	n/M	%	95% CI
Anti-PT	484/512	94.5	(92.2 ; 96.3)	507/518	97.9	(96.2 ; 98.9)	76/92	82.6	(73.3 ; 89.7)
Anti-FHA	459/512	89.6	(86.7 ; 92.1)	474/518	91.5	(88.8 ; 93.8)	57/92	62.0	(51.2 ; 71.9)

n: number of subjects with valid serology results for the particular antigen and who met the criterion.
M: Number of subjects with available data for the endpoint.
N: number of subjects in per-protocol analysis set 1, for primary series.
Pertussis vaccine seroresponse for anti-PT and anti-FHA is defined as: for a subject with a pre-primary vaccination concentration < 4 x lower level of quantitation (LLOQ), post-primary vaccination concentration must be >= 4 x LLOQ; for a subject with a pre-primary vaccination concentration >= 4 x LLOQ, post-primary vaccination concentration must be >= pre-primary vaccination concentration.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 3: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

Table 23: Summary of Pertussis vaccine seroresponse rate for anti-PT and anti-FHA at D30 after the 12 to 18-month vaccination for Groups 1 to 3 - Per-Protocol Analysis Set 2

	Group 1 (N=560)			Group 2 (N=584)			Group 3 (N=94)		
Antigens	**n/M**	**%**	**95% CI**	**n/M**	**%**	**95% CI**	**n/M**	**%**	**95% CI**
Anti-PT	517/533	97.0	(95.2 ; 98.3)	548/565	97.0	(95.2 ; 98.2)	84/90	93.3	(86.1 ; 97.5)
Anti-FHA	475/533	89.1	(86.2 ; 91.6)	509/565	90.1	(87.3 ; 92.4)	83/90	92.2	(84.6 ; 96.8)

n: number of subjects with valid serology results for the particular antigen and who met the criterion. N: number of subjects in per-protocol analysis set 2, for booster series.
Pertussis vaccine seroresponse for anti-PT and anti-FHA is defined as: for a subject with a pre-booster vaccination concentration < 4 x lower level of quantitation (LLOQ), post-booster vaccination concentration must be >= 4 x pre-booster vaccination conentration; for a subject with a pre-booster vaccination concentration >= 4 x LLOQ, post-booster vaccination concentration must be >= 2x pre-booster vaccination concentration.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 3: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

Anti-tetanus antibodies, anti-diphtheria antibodies, anti-poliovirus antibodies (types 1, 2, and 3), anti-PRP antibodies, anti-HBsAg antibody concentration, anti-pertussis antibody concentration (PT and FHA)

Table 24: Summary of geometric means of hexavalent vaccine at D30 after the 4-month vaccination for Groups 1 to 3: GMTs or GMCs - Per-Protocol Analysis Set 1

	Group 1 (N=522)			Group 2 (N=524)			Group 3 (N=96)		
Antigens	**M**	**GM**	**95% CI**	**M**	**GM**	**95% CI**	**M**	**GM**	**95% CI**
Anti-tetanus	514	1.10	(1.02 ; 1.18)	520	1.13	(1.05 ; 1.22)	93	0.931	(0.788 ; 1.10)
Anti-diphtheria	514	0.523	(0.474 ; 0.578)	520	0.489	(0.443 ; 0.541)	93	0.563	(0.458 ; 0.691)
Anti-polio 1	486	47.1	(40.1 ; 55.3)	489	43.5	(37.0 ; 51.2)	83	362	(260 ; 504)
Anti-polio 2	482	139	(117 ; 167)	485	143	(120 ; 171)	79	618	(429 ; 890)
Anti-polio 3	488	133	(112 ; 157)	492	145	(123 ; 172)	82	584	(419 ; 814)
Anti-PRP	517	0.376	(0.326 ; 0.435)	521	0.435	(0.379 ; 0.499)	96	0.725	(0.492 ; 1.07)
Anti-HBsAg	505	369	(323 ; 421)	510	345	(303 ; 393)	92	218	(147 ; 322)
Anti-PT	514	64.9	(61.4 ; 68.7)	520	68.1	(64.5 ; 72.0)	93	50.0	(43.2 ; 58.0)
Anti-FHA	514	92.4	(87.3 ; 97.8)	520	96.6	(90.8 ; 103)	93	125	(109 ; 144)

M: Number of subjects with available data for the endpoint.
N: number of subjects in per-protocol analysis set 1, for primary series.
95% CI calculated using calculation for normal distribution on log10(titer) following by antilog transformation.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 3: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

Table 25: Summary of response rate of hexavalent vaccine at D30 after the 4-month vaccination for Groups 1 to 3 - Per-Protocol Analysis Set 1

		Group 1 (N=522)			Group 2 (N=524)			Group 3 (N=96)		
Antigens	**Criterion**	**n/M**	**%**	**95% CI**	**n/M**	**%**	**95% CI**	**n/M**	**%**	**95% CI**
Anti-tetanus	>=0.01 IU/mL	514/514	100	(99.3 ; 100)	520/520	100	(99.3 ; 100)	93/93	100	(96.1 ; 100)
	>=0.1 IU/mL	514/514	100	(99.3 ; 100)	519/520	99.8	(98.9 ; 100)	93/93	100	(96.1 ; 100)
	>=1.0 IU/mL	274/514	53.3	(48.9 ; 57.7)	293/520	56.3	(52.0 ; 60.7)	41/93	44.1	(33.8 ; 54.8)
Anti-diphtheria	>=0.01 IU/mL	514/514	100	(99.3 ; 100)	519/520	99.8	(98.9 ; 100)	93/93	100	(96.1 ; 100)
	>=0.1 IU/mL	465/514	90.5	(87.6 ; 92.9)	466/520	89.6	(86.7 ; 92.1)	88/93	94.6	(87.9 ; 98.2)
	>=1.0 IU/mL	168/514	32.7	(28.6 ; 36.9)	169/520	32.5	(28.5 ; 36.7)	31/93	33.3	(23.9 ; 43.9)
Anti-polio 1	>=1:8	423/486	87.0	(83.7 ; 89.9)	407/489	83.2	(79.6 ; 86.4)	82/83	98.8	(93.5 ; 100)
Anti-polio 2	>=1:8	470/482	97.5	(95.7 ; 98.7)	478/485	98.6	(97.0 ; 99.4)	79/79	100	(95.4 ; 100)
Anti-polio 3	>=1:8	468/488	95.9	(93.7 ; 97.5)	473/492	96.1	(94.0 ; 97.7)	81/82	98.8	(93.4 ; 100)
Anti-PRP	>=0.15 ug/mL	371/517	71.8	(67.7 ; 75.6)	390/521	74.9	(70.9 ; 78.5)	75/96	78.1	(68.5 ; 85.9)
	>=1 ug/mL	125/517	24.2	(20.5 ; 28.1)	142/521	27.3	(23.5 ; 31.3)	38/96	39.6	(29.7 ; 50.1)
Anti-HBsAg	>=10 mIU/mL	487/505	96.4	(94.4 ; 97.9)	499/510	97.8	(96.2 ; 98.9)	85/92	92.4	(84.9 ; 96.9)
	>=100 mIU/mL	433/505	85.7	(82.4 ; 88.7)	417/510	81.8	(78.1 ; 85.0)	67/92	72.8	(62.6 ; 81.6)

n: Number of subjects that met the criterion
M: Number of subjects with available data for the endpoint. Percentages are based on M.
N: number of subjects in per-protocol analysis set 1, for primary series.
95% CI of the single proportion calculated from the exact binomial method.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 3: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

Table 26: Summary of geometric means of hexavalent vaccine at D0 before and at D30 the 12 to 18-month vaccination for Groups 1 to 3 - Per-Protocol Analysis Set 2

		Group 1 (N=560)			Group 2 (N=584)			Group 3 (N=94)		
Antigens	**Time Point**	**M**	**GM**	**95% CI**	**M**	**GM**	**95% CI**	**M**	**GM**	**95% CI**
Anti-tetanus	D0 before booster dose (Dose 3)	542	0.362	(0.336 ; 0.391)	571	0.424	(0.397 ; 0.453)	92	0.218	(0.180 ; 0.264)
	D30 after booster dose (Dose 3)	551	6.71	(6.33 ; 7.12)	577	8.59	(8.13 ; 9.08)	92	6.02	(5.06 ; 7.16)
Anti-diphtheria	D0 before booster dose (Dose 3)	542	0.086	(0.079 ; 0.095)	569	0.080	(0.073 ; 0.087)	91	0.094	(0.076 ; 0.116)
	D30 after booster dose (Dose 3)	551	1.82	(1.69 ; 1.96)	577	1.69	(1.57 ; 1.81)	92	2.71	(2.36 ; 3.11)
Anti-polio 1	D0 before booster dose (Dose 3)	526	14.5	(12.7 ; 16.5)	559	13.6	(12.0 ; 15.4)	89	55.2	(40.8 ; 74.6)
	D30 after booster dose (Dose 3)	533	1099	(980 ; 1233)	553	994	(883 ; 1119)	86	1538	(1212 ; 1952)
Anti-polio 2	D0 before booster dose (Dose 3)	528	33.2	(28.7 ; 38.4)	560	33.1	(28.8 ; 37.9)	88	85.3	(63.9 ; 114)
	D30 after booster dose (Dose 3)	530	2214	(1982 ; 2472)	554	2146	(1937 ; 2379)	87	3549	(2846 ; 4425)
Anti-polio 3	D0 before booster dose (Dose 3)	529	19.7	(17.1 ; 22.6)	560	18.4	(16.0 ; 21.1)	89	37.7	(27.6 ; 51.5)
	D30 after booster dose (Dose 3)	531	1595	(1393 ; 1827)	557	1533	(1361 ; 1728)	87	2431	(1897 ; 3115)
Anti-PRP	D0 before booster dose (Dose 3)	545	0.201	(0.176 ; 0.230)	571	0.224	(0.197 ; 0.255)	93	0.244	(0.174 ; 0.343)
	D30 after booster dose (Dose 3)	555	9.42	(8.31 ; 10.7)	583	11.5	(10.3 ; 12.9)	91	16.1	(11.9 ; 21.6)
Anti-HBsAg	D0 before booster dose (Dose 3)	535	53.0	(45.5 ; 61.8)	565	48.8	(42.1 ; 56.5)	91	26.0	(17.6 ; 38.2)
	D30 after booster dose (Dose 3)	546	2273	(1927 ; 2681)	571	2158	(1852 ; 2515)	90	1117	(666 ; 1872)
Anti-PT	D0 before booster dose (Dose 3)	542	14.8	(13.8 ; 15.8)	571	14.6	(13.7 ; 15.6)	92	10.4	(8.99 ; 12.0)
	D30 after booster dose (Dose 3)	551	111	(105 ; 118)	577	109	(104 ; 115)	92	79.2	(66.2 ; 94.6)
Anti-FHA	D0 before booster dose (Dose 3)	542	38.4	(35.8 ; 41.2)	571	38.1	(35.5 ; 40.8)	92	30.6	(26.0 ; 36.0)
	D30 after booster dose (Dose 3)	551	177	(167 ; 187)	577	184	(173 ; 195)	92	168	(142 ; 200)

M: Number of subjects with available data for the endpoint and time point.
N: number of subjects in per-protocol analysis set 2, for booster series.
95% CI calculated using calculation for normal distribution on log10(titer) following by antilog transformation.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 3: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

Table 27: Summary of response rate of hexavalent vaccine at D0 before and D30 after the 12 to 18-month vaccination for Groups 1 to 3 - Per-Protocol Analysis Set 2

			Group 1 (N=560)			Group 2 (N=584)			Group 3 (N=94)		
Antigens	**Criterion**	**Time Point**	**n/M**	**%**	**95% CI**	**n/M**	**%**	**95% CI**	**n/M**	**%**	**95% CI**
Anti-tetanus	>=0.01 IU/mL	D0 before booster dose (Dose 3)	542/542	100	(99.3 ; 100)	571/571	100	(99.4 ; 100)	92/92	100	(96.1 ; 100)
		D30 after booster dose (Dose 3)	551/551	100	(99.3 ; 100)	577/577	100	(99.4 ; 100)	92/92	100	(96.1 ; 100)
	>=0.1 IU/mL	D0 before booster dose (Dose 3)	510/542	94.1	(91.8 ; 95.9)	556/571	97.4	(95.7 ; 98.5)	77/92	83.7	(74.5 ; 90.6)
		D30 after booster dose (Dose 3)	551/551	100	(99.3 ; 100)	577/577	100	(99.4 ; 100)	92/92	100	(96.1 ; 100)
	>=1.0 IU/mL	D0 before booster dose (Dose 3)	58/542	10.7	(8.2 ; 13.6)	84/571	14.7	(11.9 ; 17.9)	6/92	6.5	(2.4 ; 13.7)
		D30 after booster dose (Dose 3)	549/551	99.6	(98.7 ; 100)	575/577	99.7	(98.8 ; 100)	89/92	96.7	(90.8 ; 99.3)
Anti-diphtheria	>=0.01 IU/mL	D0 before booster dose (Dose 3)	532/542	98.2	(96.6 ; 99.1)	561/569	98.6	(97.2 ; 99.4)	89/91	97.8	(92.3 ; 99.7)
		D30 after booster dose (Dose 3)	551/551	100	(99.3 ; 100)	577/577	100	(99.4 ; 100)	92/92	100	(96.1 ; 100)
	>=0.1 IU/mL	D0 before booster dose (Dose 3)	261/542	48.2	(43.9 ; 52.5)	235/569	41.3	(37.2 ; 45.5)	43/91	47.3	(36.7 ; 58.0)
		D30 after booster dose (Dose 3)	549/551	99.6	(98.7 ; 100)	576/577	99.8	(99.0 ; 100)	92/92	100	(96.1 ; 100)
	>=1.0 IU/mL	D0 before booster dose (Dose 3)	6/542	1.1	(0.4 ; 2.4)	4/569	0.7	(0.2 ; 1.8)	0/91	0	(0 ; 4.0)
		D30 after booster dose (Dose 3)	416/551	75.5	(71.7 ; 79.0)	418/577	72.4	(68.6 ; 76.1)	85/92	92.4	(84.9 ; 96.9)
Anti-polio 1	>=1:8	D0 before booster dose (Dose 3)	339/526	64.4	(60.2 ; 68.5)	356/559	63.7	(59.5 ; 67.7)	83/89	93.3	(85.9 ; 97.5)
		D30 after booster dose (Dose 3)	532/533	99.8	(99.0 ; 100)	547/553	98.9	(97.7 ; 99.6)	86/86	100	(95.8 ; 100)
Anti-polio 2	>=1:8	D0 before booster dose (Dose 3)	420/528	79.5	(75.8 ; 82.9)	453/560	80.9	(77.4 ; 84.1)	84/88	95.5	(88.8 ; 98.7)
		D30 after booster dose (Dose 3)	530/530	100	(99.3 ; 100)	554/554	100	(99.3 ; 100)	87/87	100	(95.8 ; 100)
Anti-polio 3	>=1:8	D0 before booster dose (Dose 3)	363/529	68.6	(64.5 ; 72.6)	368/560	65.7	(61.6 ; 69.6)	75/89	84.3	(75.0 ; 91.1)
		D30 after booster dose (Dose 3)	527/531	99.2	(98.1 ; 99.8)	556/557	99.8	(99.0 ; 100)	87/87	100	(95.8 ; 100)
Anti-PRP	>=0.15 ug/mL	D0 before booster dose (Dose 3)	308/545	56.5	(52.2 ; 60.7)	345/571	60.4	(56.3 ; 64.5)	56/93	60.2	(49.5 ; 70.2)
		D30 after booster dose (Dose 3)	545/555	98.2	(96.7 ; 99.1)	576/583	98.8	(97.5 ; 99.5)	91/91	100	(96.0 ; 100)
	>=1 ug/mL	D0 before booster dose (Dose 3)	76/545	13.9	(11.1 ; 17.1)	85/571	14.9	(12.1 ; 18.1)	14/93	15.1	(8.5 ; 24.0)
		D30 after booster dose (Dose 3)	508/555	91.5	(88.9 ; 93.7)	553/583	94.9	(92.7 ; 96.5)	89/91	97.8	(92.3 ; 99.7)
Anti-HBsAg	>=10 mIU/mL	D0 before booster dose (Dose 3)	436/535	81.5	(77.9 ; 84.7)	449/565	79.5	(75.9 ; 82.7)	60/91	65.9	(55.3 ; 75.5)
		D30 after booster dose (Dose 3)	535/546	98.0	(96.4 ; 99.0)	563/571	98.6	(97.3 ; 99.4)	85/90	94.4	(87.5 ; 98.2)
	>=100 mIU/mL	D0 before booster dose (Dose 3)	207/535	38.7	(34.5 ; 43.0)	200/565	35.4	(31.5 ; 39.5)	24/91	26.4	(17.7 ; 36.7)
		D30 after booster dose (Dose 3)	510/546	93.4	(91.0 ; 95.3)	534/571	93.5	(91.2 ; 95.4)	72/90	80.0	(70.2 ; 87.7)

n: number of subjects with valid serology results for the particular antigen and who met the criterion.
M: Number of subjects with available data for the endpoint and time point. Percentages are based on M.
N: number of subjects in per-protocol analysis set 2, for booster series.
95% CI of the single proportion calculated from the exact binomial method.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 3: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

Anti-pneumococcal antibody concentration against the antigens of PCV10 (Groups 1 and 2)

Table 28: Summary of geometric means of PCV10 vaccine at D30 after the 4-month vaccination for Groups 1 and 2 - Per-Protocol Analysis Set 1

		Group 1 (N=522)			Group 2 (N=524)	
Serotype	**M**	**GMC**	**95% CI**	**M**	**GMC**	**95% CI**
1	505	1.68	(1.52 ; 1.84)	512	1.71	(1.56 ; 1.87)
4	505	1.97	(1.83 ; 2.12)	512	2.06	(1.91 ; 2.23)
5	505	1.08	(0.991 ; 1.17)	512	1.10	(1.01 ; 1.19)
6B	505	0.600	(0.534 ; 0.675)	511	0.660	(0.586 ; 0.742)
7F	505	2.03	(1.89 ; 2.17)	512	2.20	(2.05 ; 2.37)
9V	504	1.67	(1.54 ; 1.81)	512	1.81	(1.67 ; 1.96)
14	505	5.92	(5.41 ; 6.48)	512	5.97	(5.44 ; 6.55)
18C	505	0.680	(0.618 ; 0.748)	512	0.796	(0.722 ; 0.879)
19F	505	1.59	(1.39 ; 1.82)	512	1.45	(1.26 ; 1.66)
23F	505	0.830	(0.746 ; 0.924)	512	0.869	(0.785 ; 0.961)

M: number of subjects with valid results for the particular serotype.
N: number of subjects in per-protocol analysis set 1, for primary series.
95% CI calculated using calculation for normal distribution on log10(titer) following by antilog transformation.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.

Table 29: Summary of geometric means of PCV10 vaccine at D30 after the 12 to 18-month vaccination for Groups 1 and 2 - Per-Protocol Analysis Set 2

	Group 1 (N=560)			Group 2 (N=584)		
Serotype	M	GMC	95% CI	M	GMC	95% CI
1	545	4.71	(4.32 ; 5.13)	569	4.54	(4.18 ; 4.94)
4	545	3.61	(3.37 ; 3.86)	569	3.19	(2.99 ; 3.41)
5	544	2.21	(2.05 ; 2.39)	569	2.05	(1.90 ; 2.20)
6B	545	4.21	(3.89 ; 4.55)	569	4.36	(4.04 ; 4.71)
7F	545	2.91	(2.73 ; 3.10)	568	2.89	(2.70 ; 3.10)
9V	545	4.08	(3.80 ; 4.38)	569	4.17	(3.89 ; 4.47)
14	544	9.07	(8.44 ; 9.75)	568	7.89	(7.25 ; 8.59)
18C	545	2.12	(1.99 ; 2.26)	569	2.17	(2.03 ; 2.33)
19F	545	9.03	(8.32 ; 9.81)	569	8.41	(7.76 ; 9.12)
23F	545	2.24	(2.10 ; 2.40)	569	2.04	(1.90 ; 2.18)

M: number of subjects with valid results for the particular serotype.
N: number of subjects in per-protocol analysis set 2, for booster series.
95% CI calculated using calculation for normal distribution on log10(titer) following by antilog transformation.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.

Table 30: Summary of response rate of PCV10 vaccine at D30 after the 4-month vaccination for Groups 1 and 2 - Per-Protocol Analysis Set 1

		Group 1 (N=522)			Group 2 (N=524)		
Serotype	Criterion	n/M	%	95% CI	n/M	%	95% CI
1	>=0.35 ug/mL	468/505	92.7	(90.0 ; 94.8)	479/512	93.6	(91.1 ; 95.5)
	>=1 ug/mL	370/505	73.3	(69.2 ; 77.1)	372/512	72.7	(68.6 ; 76.5)
4	>=0.35 ug/mL	489/505	96.8	(94.9 ; 98.2)	495/512	96.7	(94.7 ; 98.1)
	>=1 ug/mL	409/505	81.0	(77.3 ; 84.3)	426/512	83.2	(79.7 ; 86.3)
5	>=0.35 ug/mL	447/505	88.5	(85.4 ; 91.2)	464/512	90.6	(87.8 ; 93.0)
	>=1 ug/mL	293/505	58.0	(53.6 ; 62.4)	294/512	57.4	(53.0 ; 61.7)
6B	>=0.35 ug/mL	339/505	67.1	(62.8 ; 71.2)	357/511	69.9	(65.7 ; 73.8)
	>=1 ug/mL	191/505	37.8	(33.6 ; 42.2)	224/511	43.8	(39.5 ; 48.3)
7F	>=0.35 ug/mL	499/505	98.8	(97.4 ; 99.6)	503/512	98.2	(96.7 ; 99.2)
	>=1 ug/mL	417/505	82.6	(79.0 ; 85.8)	438/512	85.5	(82.2 ; 88.5)
9V	>=0.35 ug/mL	477/504	94.6	(92.3 ; 96.4)	487/512	95.1	(92.9 ; 96.8)
	>=1 ug/mL	370/504	73.4	(69.3 ; 77.2)	393/512	76.8	(72.9 ; 80.4)
14	>=0.35 ug/mL	494/505	97.8	(96.1 ; 98.9)	503/512	98.2	(96.7 ; 99.2)
	>=1 ug/mL	479/505	94.9	(92.5 ; 96.6)	479/512	93.6	(91.1 ; 95.5)
18C	>=0.35 ug/mL	366/505	72.5	(68.4 ; 76.3)	396/512	77.3	(73.5 ; 80.9)
	>=1 ug/mL	201/505	39.8	(35.5 ; 44.2)	219/512	42.8	(38.4 ; 47.2)
19F	>=0.35 ug/mL	415/505	82.2	(78.6 ; 85.4)	406/512	79.3	(75.5 ; 82.7)
	>=1 ug/mL	347/505	68.7	(64.5 ; 72.7)	320/512	62.5	(58.1 ; 66.7)
23F	>=0.35 ug/mL	393/505	77.8	(73.9 ; 81.4)	411/512	80.3	(76.6 ; 83.6)
	>=1 ug/mL	245/505	48.5	(44.1 ; 53.0)	256/512	50.0	(45.6 ; 54.4)

n: Number of subjects with anti-pneumococcal antibodies concentrations that met the criterion.
M: Number of subjects with available data for the endpoint. Percentages are based on M.
N: number of subjects in per-protocol analysis set 1, for primary series.
95% CI of the single proportion calculated from the exact binomial method.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.

Table 31: Summary of response rate of PCV10 vaccine at D30 after the 12 to 18-month vaccination for Groups 1 and 2 - Per-Protocol Analysis Set 2

		Group 1 (N=560)			Group 2 (N=584)		
Serotype	Criterion	n/M	%	95% CI	n/M	%	95% CI
1	>=0.35 ug/mL	544/545	99.8	(99.0 ; 100)	568/569	99.8	(99.0 ; 100)
	>=1 ug/mL	509/545	93.4	(91.0 ; 95.3)	526/569	92.4	(90.0 ; 94.5)
4	>=0.35 ug/mL	544/545	99.8	(99.0 ; 100)	567/569	99.6	(98.7 ; 100)
	>=1 ug/mL	523/545	96.0	(94.0 ; 97.5)	528/569	92.8	(90.4 ; 94.8)
5	>=0.35 ug/mL	534/544	98.2	(96.6 ; 99.1)	556/569	97.7	(96.1 ; 98.8)
	>=1 ug/mL	444/544	81.6	(78.1 ; 84.8)	448/569	78.7	(75.1 ; 82.0)
6B	>=0.35 ug/mL	539/545	98.9	(97.6 ; 99.6)	566/569	99.5	(98.5 ; 99.9)
	>=1 ug/mL	514/545	94.3	(92.0 ; 96.1)	534/569	93.8	(91.5 ; 95.7)
7F	>=0.35 ug/mL	543/545	99.6	(98.7 ; 100)	564/568	99.3	(98.2 ; 99.8)
	>=1 ug/mL	509/545	93.4	(91.0 ; 95.3)	532/568	93.7	(91.3 ; 95.5)
9V	>=0.35 ug/mL	544/545	99.8	(99.0 ; 100)	568/569	99.8	(99.0 ; 100)
	>=1 ug/mL	521/545	95.6	(93.5 ; 97.2)	540/569	94.9	(92.8 ; 96.6)
14	>=0.35 ug/mL	544/544	100	(99.3 ; 100)	564/568	99.3	(98.2 ; 99.8)
	>=1 ug/mL	539/544	99.1	(97.9 ; 99.7)	550/568	96.8	(95.0 ; 98.1)
18C	>=0.35 ug/mL	540/545	99.1	(97.9 ; 99.7)	561/569	98.6	(97.2 ; 99.4)
	>=1 ug/mL	461/545	84.6	(81.3 ; 87.5)	485/569	85.2	(82.1 ; 88.1)
19F	>=0.35 ug/mL	541/545	99.3	(98.1 ; 99.8)	565/569	99.3	(98.2 ; 99.8)
	>=1 ug/mL	531/545	97.4	(95.7 ; 98.6)	562/569	98.8	(97.5 ; 99.5)

23F	>=0.35 ug/mL	537/545	98.5	(97.1 ; 99.4)	553/569	97.2	(95.5 ; 98.4)
	>=1 ug/mL	467/545	85.7	(82.5 ; 88.5)	468/569	82.2	(78.9 ; 85.3)

n: Number of subjects with anti-pneumococcal antibodies concentrations that met the criterion.
M: Number of subjects with available data for the endpoint. Percentages are based on M.
N: number of subjects in per-protocol analysis set 2, for booster series.
95% CI of the single proportion calculated from the exact binomial method.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.

Anti-pneumococcal antibody concentration against the antigens of PCV13 (Group 3)

Table 32: Summary of geometric means of PCV13 vaccine at D30 after the 4-month vaccination for Group 3 - Per-Protocol Analysis Set 1

Serotype	M	Group 3 (N=96) GMC	95% CI
1	89	1.47	(1.16 ; 1.87)
3	89	0.658	(0.554 ; 0.781)
4	89	1.73	(1.42 ; 2.12)
5	89	0.803	(0.617 ; 1.04)
6A	89	1.65	(1.24 ; 2.19)
6B	89	0.275	(0.205 ; 0.368)
7F	89	3.04	(2.59 ; 3.57)
9V	89	1.25	(0.987 ; 1.59)
14	89	5.88	(4.31 ; 8.01)
18C	89	1.65	(1.30 ; 2.10)
19A	89	2.17	(1.67 ; 2.80)
19F	89	5.73	(4.64 ; 7.08)
23F	89	0.722	(0.552 ; 0.945)

M: number of subjects with valid results for the particular serotype.
N: number of subjects in per-protocol analysis set 1, for primary series.
95% CI calculated using calculation for normal distribution on log10(titer) following by antilog transformation.
Group 3: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

Table 33: Summary of geometric means of PCV13 vaccine at D30 after the 12 to 18-month vaccination for Group 3 - Per-Protocol Analysis Set 2

Serotype	M	Group 3 (N=94) GMC	95% CI
1	91	5.32	(4.41 ; 6.42)
3	91	1.13	(0.945 ; 1.35)
4	91	3.99	(3.43 ; 4.64)
5	91	3.33	(2.75 ; 4.03)
6A	91	12.9	(10.9 ; 15.4)
6B	91	7.01	(5.38 ; 9.13)
7F	91	5.36	(4.56 ; 6.29)
9V	91	5.12	(4.26 ; 6.17)
14	91	14.8	(12.2 ; 18.1)
18C	91	3.18	(2.70 ; 3.76)
19A	91	8.82	(7.25 ; 10.7)
19F	91	12.1	(9.91 ; 14.7)
23F	91	3.70	(3.01 ; 4.55)

M: number of subjects with valid results for the particular serotype.
N: number of subjects in per-protocol analysis set 2, for booster series.
95% CI calculated using calculation for normal distribution on log10(titer) following by antilog transformation.
Group 3: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

Table 34: Summary of response rate of PCV13 vaccine at D30 after the 4-month vaccination for Group 3 - Per-Protocol Analysis Set 1

Serotype	Criterion	n/M	Group 3 (N=96) %	95% CI
1	>=0.35 ug/mL	80/89	89.9	(81.7 ; 95.3)
	>=1 ug/mL	59/89	66.3	(55.5 ; 76.0)
3	>=0.35 ug/mL	73/89	82.0	(72.5 ; 89.4)
	>=1 ug/mL	30/89	33.7	(24.0 ; 44.5)
4	>=0.35 ug/mL	86/89	96.6	(90.5 ; 99.3)
	>=1 ug/mL	68/89	76.4	(66.2 ; 84.8)
5	>=0.35 ug/mL	68/89	76.4	(66.2 ; 84.8)
	>=1 ug/mL	47/89	52.8	(41.9 ; 63.5)
6A	>=0.35 ug/mL	79/89	88.8	(80.3 ; 94.5)
	>=1 ug/mL	59/89	66.3	(55.5 ; 76.0)
6B	>=0.35 ug/mL	36/89	40.4	(30.2 ; 51.4)
	>=1 ug/mL	18/89	20.2	(12.4 ; 30.1)
7F	>=0.35 ug/mL	87/89	97.8	(92.1 ; 99.7)
	>=1 ug/mL	83/89	93.3	(85.9 ; 97.5)
9V	>=0.35 ug/mL	79/89	88.8	(80.3 ; 94.5)
	>=1 ug/mL	54/89	60.7	(49.7 ; 70.9)
14	>=0.35 ug/mL	86/89	96.6	(90.5 ; 99.3)
	>=1 ug/mL	78/89	87.6	(79.0 ; 93.7)
18C	>=0.35 ug/mL	81/89	91.0	(83.1 ; 96.0)
	>=1 ug/mL	63/89	70.8	(60.2 ; 79.9)
19A	>=0.35 ug/mL	83/89	93.3	(85.9 ; 97.5)
	>=1 ug/mL	69/89	77.5	(67.4 ; 85.7)
19F	>=0.35 ug/mL	88/89	98.9	(93.9 ; 100)
	>=1 ug/mL	84/89	94.4	(87.4 ; 98.2)
23F	>=0.35 ug/mL	64/89	71.9	(61.4 ; 80.9)
	>=1 ug/mL	34/89	38.2	(28.1 ; 49.1)

n: Number of subjects with anti-pneumococcal antibodies concentrations that met the criterion.
M: Number of subjects with available data for the endpoint. Percentages are based on M.
N: number of subjects in per-protocol analysis set 1, for primary series.
95% CI of the single proportion calculated from the exact binomial method.
Group 3: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

Table 35: Summary of response rate of PCV13 vaccine at D30 after the 12 to 18-month vaccination for Group 3 - Per-Protocol Analysis Set 2

Serotype	Criterion	n/M	Group 3 (N=94) %	95% CI
1	>=0.35 ug/mL	91/91	100	(96.0 ; 100)
	>=1 ug/mL	87/91	95.6	(89.1 ; 98.8)
3	>=0.35 ug/mL	89/91	97.8	(92.3 ; 99.7)
	>=1 ug/mL	47/91	51.6	(40.9 ; 62.3)
4	>=0.35 ug/mL	91/91	100	(96.0 ; 100)
	>=1 ug/mL	90/91	98.9	(94.0 ; 100)
5	>=0.35 ug/mL	90/91	98.9	(94.0 ; 100)
	>=1 ug/mL	85/91	93.4	(86.2 ; 97.5)
6A	>=0.35 ug/mL	91/91	100	(96.0 ; 100)
	>=1 ug/mL	91/91	100	(96.0 ; 100)
6B	>=0.35 ug/mL	90/91	98.9	(94.0 ; 100)
	>=1 ug/mL	84/91	92.3	(84.8 ; 96.9)
7F	>=0.35 ug/mL	91/91	100	(96.0 ; 100)
	>=1 ug/mL	91/91	100	(96.0 ; 100)
9V	>=0.35 ug/mL	91/91	100	(96.0 ; 100)
	>=1 ug/mL	89/91	97.8	(92.3 ; 99.7)
14	>=0.35 ug/mL	91/91	100	(96.0 ; 100)
	>=1 ug/mL	91/91	100	(96.0 ; 100)
18C	>=0.35 ug/mL	91/91	100	(96.0 ; 100)
	>=1 ug/mL	85/91	93.4	(86.2 ; 97.5)
19A	>=0.35 ug/mL	91/91	100	(96.0 ; 100)
	>=1 ug/mL	90/91	98.9	(94.0 ; 100)
19F	>=0.35 ug/mL	91/91	100	(96.0 ; 100)
	>=1 ug/mL	91/91	100	(96.0 ; 100)
23F	>=0.35 ug/mL	91/91	100	(96.0 ; 100)
	>=1 ug/mL	84/91	92.3	(84.8 ; 96.9)

n: Number of subjects with anti-pneumococcal antibodies concentrations that met the criterion.
M: Number of subjects with available data for the endpoint. Percentages are based on M.
N: number of subjects in per-protocol analysis set 2, for booster series.
95% CI of the single proportion calculated from the exact binomial method.
Group 3: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

Anti-measles, anti-mumps, and anti-rubella antibody concentration

Table 36: Summary of geometric means of MMR vaccine at D30 after the 12 to 18-month vaccination for Groups 1 to 3 - Per-Protocol Analysis Set 2

		Group 1 (N=560)			Group 2 (N=584)			Group 3 (N=94)	
Antigens	M	GMC	95% CI	M	GMC	95% CI	M	GMC	95% CI
Anti-measles	525	2780	(2581 ; 2995)	553	2919	(2739 ; 3110)	94	3457	(2972 ; 4021)
Anti-mumps	525	83.3	(77.5 ; 89.6)	553	86.1	(80.5 ; 92.1)	94	105	(90.4 ; 121)
Anti-rubella	525	56.8	(53.2 ; 60.6)	553	56.0	(52.5 ; 59.8)	94	72.8	(62.7 ; 84.6)

M: Number of subjects with available data for the endpoint when the MMR vaccine has been administered concomitantly with the study vaccines.
N: number of subjects in per-protocol analysis set 2, for booster series.
95% CI calculated using calculation for normal distribution on log10(titer) following by antilog transformation.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 3: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

Table 37: Summary of response rate of MMR vaccine at D30 after the 12 to 18-month vaccination for Groups 1 to 3 - Per-Protocol Analysis Set 2

		Group 1 (N=560)			Group 2 (N=584)			Group 3 (N=94)		
Antigens	Serostatus cutoff	n/M	%	95% CI	n/M	%	95% CI	n/M	%	95% CI
Anti-measles	>=255 mIU/mL	516/525	98.3	(96.8 ; 99.2)	548/553	99.1	(97.9 ; 99.7)	94/94	100	(96.2 ; 100)
Anti-mumps	>=10 Mumps Ab units/mL	518/525	98.7	(97.3 ; 99.5)	546/553	98.7	(97.4 ; 99.5)	94/94	100	(96.2 ; 100)
Anti-rubella	>=10 IU/mL	518/525	98.7	(97.3 ; 99.5)	538/553	97.3	(95.6 ; 98.5)	93/94	98.9	(94.2 ; 100)

n: Number of subjects experiencing the endpoint listed in the first and second columns and met the criterion.
M: Number of subjects with available data for the endpoint when the MMR vaccine has been administered concomitantly with the study vaccines. Percentages are based on M.
N: number of subjects in per-protocol analysis set 2, for booster series.
95% CI of the single proportion calculated from the exact binomial method.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 3: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

Secondary Objective #4: hSBA Antibody Responses Against the Meningococcal A, C, W, and Y Serogroups in a 3-dose Series of MenACYW Conjugate Vaccine Versus Nimenrix (Groups 1 and 2)

hSBA Antibody GMTs (Groups 1 and 2)

Table 38: Summary of geometric means of hSBA titres at D0 before the 2-month vaccination and at D30 after the 4-month vaccination for Groups 1 and 2 - Per-Protocol Analysis Set 1

			Group 1 (N=522)			Group 2 (N=524)	
Serogroup	Time Point	M	GMT	95% CI	M	GMT	95% CI
A	D0 before dose 1	521	2.60	(2.50 ; 2.70)	519	2.58	(2.48 ; 2.69)
	D30 after dose 2	508	11.6	(10.3 ; 13.2)	508	18.9	(16.7 ; 21.5)
C	D0 before dose 1	517	2.39	(2.28 ; 2.51)	517	2.40	(2.28 ; 2.52)
	D30 after dose 2	513	322	(290 ; 357)	521	73.4	(64.5 ; 83.5)
Y	D0 before dose 1	519	2.36	(2.24 ; 2.49)	518	2.32	(2.21 ; 2.42)
	D30 after dose 2	516	44.7	(40.6 ; 49.1)	523	32.8	(29.8 ; 36.2)
W	D0 before dose 1	520	2.25	(2.18 ; 2.33)	520	2.23	(2.16 ; 2.29)
	D30 after dose 2	518	66.1	(59.6 ; 73.2)	523	47.2	(42.6 ; 52.3)

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, for primary series.
95% CI calculated using calculation for normal distribution on log10(titer) following by antilog transformation.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix ® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.

Table 39: Summary of geometric means of hSBA titres at D0 before and at D30 after the 12 to 18-month vaccination for Groups 1 and 2 - Per-Protocol Analysis Set 2

		Group 1 (N=560)			Group 2 (N=584)		
Serogroup	**Time Point**	**M**	**GMT**	**95% CI**	**M**	**GMT**	**95% CI**
A	D0 before booster dose (Dose 3)	540	4.92	(4.56 ; 5.31)	567	6.79	(6.16 ; 7.49)
	D30 after booster dose (Dose 3)	543	131	(113 ; 151)	567	189	(165 ; 218)
C	D0 before booster dose (Dose 3)	545	32.1	(28.5 ; 36.2)	572	5.91	(5.36 ; 6.51)
	D30 after booster dose (Dose 3)	550	565	(505 ; 632)	578	120	(106 ; 135)
Y	D0 before booster dose (Dose 3)	545	23.4	(21.3 ; 25.8)	572	11.1	(10.1 ; 12.2)
	D30 after booster dose (Dose 3)	554	285	(260 ; 313)	579	160	(145 ; 177)
W	D0 before booster dose (Dose 3)	541	32.4	(29.0 ; 36.2)	567	16.2	(14.6 ; 17.9)
	D30 after booster dose (Dose 3)	547	423	(382 ; 468)	575	275	(247 ; 305)

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, for booster series.
95% CI calculated using calculation for normal distribution on log10(titer) following by antilog transformation.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix ® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.

hSBA Antibody Titres >= 1:4 and ≥ 1:8 (Groups 1 and 2)

Table 40: Distribution of hSBA titres at D0 before the 2-month vaccination and at D30 after the 4-month vaccination for Groups 1 and 2 - Per-Protocol Analysis Set 1

			Group 1 (N=522)		Group 2 (N=524)	
Serogroup	**Time Point**	**hSBA Titers**	**n/M**	**%**	**n/M**	**%**
A	D0 before dose 1	<1:4	359/521	68.9	372/519	71.7
		>=1:4	162/521	31.1	147/519	28.3
		>=1:8	29/521	5.6	33/519	6.4
		>=1:16	5/521	1.0	6/519	1.2
		>=1:32	1/521	0.2	4/519	0.8
		>=1:64	0/521	0	1/519	0.2
	D30 after dose 2	<1:4	116/508	22.8	61/508	12.0
		>=1:4	392/508	77.2	447/508	88.0
		>=1:8	323/508	63.6	385/508	75.8
		>=1:16	243/508	47.8	316/508	62.2
		>=1:32	165/508	32.5	231/508	45.5
		>=1:64	101/508	19.9	143/508	28.1
		>=1:128	44/508	8.7	73/508	14.4
		>=1:256	16/508	3.1	36/508	7.1
		>=1:512	5/508	1.0	13/508	2.6
		>=1:1024	2/508	0.4	3/508	0.6
C	D0 before dose 1	<1:4	443/517	85.7	440/517	85.1
		>=1:4	74/517	14.3	77/517	14.9
		>=1:8	27/517	5.2	27/517	5.2
		>=1:16	17/517	3.3	13/517	2.5
		>=1:32	8/517	1.5	10/517	1.9
		>=1:64	4/517	0.8	4/517	0.8
		>=1:128	3/517	0.6	3/517	0.6
		>=1:256	1/517	0.2	1/517	0.2
	D30 after dose 2	<1:4	5/513	1.0	19/521	3.6
		>=1:4	508/513	99.0	502/521	96.4
		>=1:8	507/513	98.8	479/521	91.9
		>=1:16	505/513	98.4	458/521	87.9
		>=1:32	495/513	96.5	416/521	79.8
		>=1:64	481/513	93.8	351/521	67.4
		>=1:128	450/513	87.7	272/521	52.2
		>=1:256	386/513	75.2	148/521	28.4
		>=1:512	275/513	53.6	62/521	11.9
		>=1:1024	134/513	26.1	18/521	3.5
		>=1:2048	15/513	2.9	1/521	0.2
		>=1:4096	4/513	0.8	1/521	0.2
Y	D0 before dose 1	<1:4	467/519	90.0	467/518	90.2
		>=1:4	52/519	10.0	51/518	9.8

		>=1:8	33/519	6.4	29/518	5.6
		>=1:16	17/519	3.3	19/518	3.7
		>=1:32	12/519	2.3	8/518	1.5
		>=1:64	4/519	0.8	2/518	0.4
		>=1:128	3/519	0.6	1/518	0.2
		>=1:256	2/519	0.4	0/518	0
		>=1:512	1/519	0.2	0/518	0
	D30 after dose 2	<1:4	9/516	1.7	14/523	2.7
		>=1:4	507/516	98.3	509/523	97.3
		>=1:8	498/516	96.5	489/523	93.5
		>=1:16	462/516	89.5	439/523	83.9
		>=1:32	388/516	75.2	330/523	63.1
		>=1:64	264/516	51.2	218/523	41.7
		>=1:128	136/516	26.4	89/523	17.0
		>=1:256	44/516	8.5	26/523	5.0
		>=1:512	10/516	1.9	9/523	1.7
		>=1:1024	3/516	0.6	2/523	0.4
W	D0 before dose 1	<1:4	459/520	88.3	463/520	89.0
		>=1:4	61/520	11.7	57/520	11.0
		>=1:8	19/520	3.7	18/520	3.5
		>=1:16	5/520	1.0	3/520	0.6
		>=1:32	2/520	0.4	1/520	0.2
		>=1:64	1/520	0.2	1/520	0.2
		>=1:128	1/520	0.2	0/520	0
	D30 after dose 2	<1:4	7/518	1.4	9/523	1.7
		>=1:4	511/518	98.6	514/523	98.3
		>=1:8	500/518	96.5	494/523	94.5
		>=1:16	482/518	93.1	465/523	88.9
		>=1:32	436/518	84.2	391/523	74.8
		>=1:64	335/518	64.7	279/523	53.3
		>=1:128	208/518	40.2	165/523	31.5
		>=1:256	101/518	19.5	58/523	11.1
		>=1:512	35/518	6.8	16/523	3.1
		>=1:1024	6/518	1.2	3/523	0.6

n: number of subjects experiencing the endpoint listed in the first 3 columns
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, for primary series.
Percentages are based on M.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.

Table 41: Number and percentage of subjects with >= 4-fold rise of hSBA titre from pre-2-month vaccination to D30 after the 4-month vaccination for Groups 1 and 2 - Per-Protocol Analysis Set 1

	Group 1 (N=522)			Group 2 (N=524)		
Serogroup	**n/M**	**%**	**95% CI**	**n/M**	**%**	**95% CI**
A	290/507	57.2	(52.8 ; 61.6)	355/504	70.4	(66.2 ; 74.4)
C	496/508	97.6	(95.9 ; 98.8)	459/514	89.3	(86.3 ; 91.8)
Y	481/513	93.8	(91.3 ; 95.7)	467/517	90.3	(87.4 ; 92.7)
W	494/516	95.7	(93.6 ; 97.3)	484/519	93.3	(90.7 ; 95.3)

n: number of subjects with valid serology results for the particular serogroup and who met the criterion.
M: number of subjects with valid serology results for the particular serogroup.
N: number of subjects in per-protocol analysis set 1, for primary series.
Percentages are based on M.
95% CI of the single proportion calculated from the exact binomial method.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.

Table 42: Distribution of hSBA titres at D0 before and at D30 after the 12 to 18-month vaccination for Groups 1 and 2 - Per-Protocol Analysis Set 2

			Group 1 (N=560)		Group 2 (N=584)	
Serogroup	**Time Point**	**hSBA Titers**	**n/M**	**%**	**n/M**	**%**
A	D0 before booster dose (Dose 3)	<1:4	167/540	30.9	149/567	26.3
		>=1:4	373/540	69.1	418/567	73.7
		>=1:8	182/540	33.7	262/567	46.2
		>=1:16	84/540	15.6	153/567	27.0
		>=1:32	40/540	7.4	85/567	15.0
		>=1:64	16/540	3.0	45/567	7.9
		>=1:128	6/540	1.1	23/567	4.1
		>=1:256	0/540	0	10/567	1.8
		>=1:512	0/540	0	3/567	0.5
		>=1:1024	0/540	0	1/567	0.2
	D30 after booster dose (Dose 3)	<1:4	10/543	1.8	11/567	1.9
		>=1:4	533/543	98.2	556/567	98.1
		>=1:8	514/543	94.7	547/567	96.5
		>=1:16	493/543	90.8	524/567	92.4
		>=1:32	460/543	84.7	499/567	88.0
		>=1:64	397/543	73.1	456/567	80.4
		>=1:128	338/543	62.2	400/567	70.5
		>=1:256	255/543	47.0	331/567	58.4
		>=1:512	160/543	29.5	228/567	40.2
		>=1:1024	90/543	16.6	130/567	22.9
		>=1:2048	17/543	3.1	26/567	4.6
		>=1:4096	11/543	2.0	17/567	3.0
		>=1:8192	5/543	0.9	5/567	0.9
		>=1:16384	1/543	0.2	3/567	0.5
C	D0 before booster dose (Dose 3)	<1:4	41/545	7.5	217/572	37.9
		>=1:4	504/545	92.5	355/572	62.1
		>=1:8	480/545	88.1	238/572	41.6
		>=1:16	426/545	78.2	160/572	28.0
		>=1:32	331/545	60.7	83/572	14.5
		>=1:64	229/545	42.0	38/572	6.6
		>=1:128	130/545	23.9	11/572	1.9
		>=1:256	56/545	10.3	5/572	0.9
		>=1:512	24/545	4.4	1/572	0.2
		>=1:1024	3/545	0.6	1/572	0.2
		>=1:2048	0/545	0	1/572	0.2
		>=1:4096	0/545	0	1/572	0.2
	D30 after booster dose (Dose 3)	<1:4	1/550	0.2	11/578	1.9
		>=1:4	549/550	99.8	567/578	98.1
		>=1:8	548/550	99.6	552/578	95.5
		>=1:16	547/550	99.5	532/578	92.0
		>=1:32	544/550	98.9	496/578	85.8
		>=1:64	531/550	96.5	444/578	76.8
		>=1:128	503/550	91.5	356/578	61.6
		>=1:256	452/550	82.2	252/578	43.6
		>=1:512	372/550	67.6	152/578	26.3
		>=1:1024	248/550	45.1	51/578	8.8
		>=1:2048	104/550	18.9	6/578	1.0
		>=1:4096	45/550	8.2	3/578	0.5
		>=1:8192	22/550	4.0	0/578	0
		>=1:16384	8/550	1.5	0/578	0
		>=1:32768	4/550	0.7	0/578	0
		>=1:65536	1/550	0.2	0/578	0
Y	D0 before booster dose (Dose 3)	<1:4	23/545	4.2	82/572	14.3
		>=1:4	522/545	95.8	490/572	85.7
		>=1:8	479/545	87.9	398/572	69.6
		>=1:16	414/545	76.0	291/572	50.9
		>=1:32	288/545	52.8	153/572	26.7
		>=1:64	154/545	28.3	58/572	10.1
		>=1:128	58/545	10.6	22/572	3.8
		>=1:256	14/545	2.6	2/572	0.3
		>=1:512	5/545	0.9	0/572	0
	D30 after booster dose (Dose 3)	<1:4	0/554	0	0/579	0
		>=1:4	554/554	100	579/579	100
		>=1:8	554/554	100	578/579	99.8
		>=1:16	553/554	99.8	565/579	97.6
		>=1:32	542/554	97.8	538/579	92.9
		>=1:64	526/554	94.9	489/579	84.5
		>=1:128	466/554	84.1	398/579	68.7
		>=1:256	361/554	65.2	278/579	48.0
		>=1:512	256/554	46.2	173/579	29.9
		>=1:1024	128/554	23.1	59/579	10.2
		>=1:2048	16/554	2.9	3/579	0.5
		>=1:4096	7/554	1.3	0/579	0
		>=1:8192	1/554	0.2	0/579	0
W	D0 before booster dose (Dose 3)	<1:4	18/541	3.3	50/567	8.8
		>=1:4	523/541	96.7	517/567	91.2

	>=1:8	482/541	89.1	440/567	77.6
	>=1:16	424/541	78.4	339/567	59.8
	>=1:32	331/541	61.2	234/567	41.3
	>=1:64	230/541	42.5	121/567	21.3
	>=1:128	116/541	21.4	48/567	8.5
	>=1:256	48/541	8.9	8/567	1.4
	>=1:512	17/541	3.1	2/567	0.4
	>=1:1024	2/541	0.4	0/567	0
D30 after booster dose (Dose 3)	<1:4	0/547	0	0/575	0
	>=1:4	547/547	100	575/575	100
	>=1:8	546/547	99.8	572/575	99.5
	>=1:16	544/547	99.5	568/575	98.8
	>=1:32	539/547	98.5	556/575	96.7
	>=1:64	527/547	96.3	523/575	91.0
	>=1:128	480/547	87.8	461/575	80.2
	>=1:256	425/547	77.7	385/575	67.0
	>=1:512	332/547	60.7	264/575	45.9
	>=1:1024	209/547	38.2	137/575	23.8
	>=1:2048	51/547	9.3	30/575	5.2
	>=1:4096	18/547	3.3	8/575	1.4
	>=1:8192	6/547	1.1	3/575	0.5
	>=1:16384	1/547	0.2	1/575	0.2

n: number of subjects experiencing the endpoint listed in the first 3 columns
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, for booster series.
Percentages are based on M.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.

Table 43: Percentage of subjects with hSBA titre >= 1:4 and >= 1:8 at D0 before and at D30 after the 12 to 18-month vaccination for Groups 1 and 2 - Per-Protocol Analysis Set 2

			Group 1 (N=560)			Group 2 (N=584)		
Serogroup	**Time Point**	**hSBA Titers**	**n/M**	**%**	**95% CI**	**n/M**	**%**	**95% CI**
A	D0 before booster dose (Dose 3)	>=1:4	373/540	69.1	(65.0 ; 73.0)	418/567	73.7	(69.9 ; 77.3)
		>=1:8	182/540	33.7	(29.7 ; 37.9)	262/567	46.2	(42.0 ; 50.4)
	D30 after booster dose (Dose 3)	>=1:4	533/543	98.2	(96.6 ; 99.1)	556/567	98.1	(96.6 ; 99.0)
		>=1:8	514/543	94.7	(92.4 ; 96.4)	547/567	96.5	(94.6 ; 97.8)
C	D0 before booster dose (Dose 3)	>=1:4	504/545	92.5	(89.9 ; 94.5)	355/572	62.1	(57.9 ; 66.1)
		>=1:8	480/545	88.1	(85.1 ; 90.7)	238/572	41.6	(37.5 ; 45.8)
	D30 after booster dose (Dose 3)	>=1:4	549/550	99.8	(99.0 ; 100)	567/578	98.1	(96.6 ; 99.0)
		>=1:8	548/550	99.6	(98.7 ; 100)	552/578	95.5	(93.5 ; 97.0)
Y	D0 before booster dose (Dose 3)	>=1:4	522/545	95.8	(93.7 ; 97.3)	490/572	85.7	(82.5 ; 88.4)
		>=1:8	479/545	87.9	(84.9 ; 90.5)	398/572	69.6	(65.6 ; 73.3)
	D30 after booster dose (Dose 3)	>=1:4	554/554	100	(99.3 ; 100)	579/579	100	(99.4 ; 100)
		>=1:8	554/554	100	(99.3 ; 100)	578/579	99.8	(99.0 ; 100)
W	D0 before booster dose (Dose 3)	>=1:4	523/541	96.7	(94.8 ; 98.0)	517/567	91.2	(88.5 ; 93.4)
		>=1:8	482/541	89.1	(86.2 ; 91.6)	440/567	77.6	(73.9 ; 81.0)
	D30 after booster dose (Dose 3)	>=1:4	547/547	100	(99.3 ; 100)	575/575	100	(99.4 ; 100)
		>=1:8	546/547	99.8	(99.0 ; 100)	572/575	99.5	(98.5 ; 99.9)

n: number of subjects experiencing the endpoint listed in the first 3 columns.
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, for booster series.
95% CI of the single proportion calculated from the exact binomial method.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix ® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.

hSBA Antibody Titres >= 4-Fold Rise Increase (Groups 1 and 2)

Table 44: Number and percentage of subjects with >= 4-fold rise of hSBA titre from pre-2-month vaccination to D30 after the 4-month vaccination for Groups 1 and 2 - Per-Protocol Analysis Set 1

	Group 1 (N=522)			Group 2 (N=524)		
Serogroup	**n/M**	**%**	**95% CI**	**n/M**	**%**	**95% CI**
A	290/507	57.2	(52.8 ; 61.6)	355/504	70.4	(66.2 ; 74.4)
C	496/508	97.6	(95.9 ; 98.8)	459/514	89.3	(86.3 ; 91.8)
Y	481/513	93.8	(91.3 ; 95.7)	467/517	90.3	(87.4 ; 92.7)
W	494/516	95.7	(93.6 ; 97.3)	484/519	93.3	(90.7 ; 95.3)

n: number of subjects with valid serology results for the particular serogroup and who met the criterion.
M: number of subjects with valid serology results for the particular serogroup.
N: number of subjects in per-protocol analysis set 1, for primary series.
Percentages are based on M.
95% CI of the single proportion calculated from the exact binomial method.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.

Table 45: Number and percentage of subjects with >= 4-fold rise of hSBA titre from pre-2-month vaccination to D30 after the 12 to 18-month vaccination for Groups 1 and 2 - Per-Protocol Analysis Set 2

	Group 1 (N=560)			Group 2 (N=584)		
Serogroup	**n/M**	**%**	**95% CI**	**n/M**	**%**	**95% CI**
A	508/542	93.7	(91.3 ; 95.6)	534/564	94.7	(92.5 ; 96.4)
C	539/545	98.9	(97.6 ; 99.6)	540/573	94.2	(92.0 ; 96.0)
Y	545/551	98.9	(97.6 ; 99.6)	568/575	98.8	(97.5 ; 99.5)
W	544/545	99.8	(99.0 ; 100)	567/572	99.1	(98.0 ; 99.7)

n: number of subjects with valid serology results for the particular serogroup and who met the criterion.
M: number of subjects with valid serology results for the particular serogroup and time period.
N: number of subjects in per-protocol analysis set 2, for booster series.
Percentages are based on M.
95% CI of the single proportion calculated from the exact binomial method.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.

Table 46: Number and percentage of subjects with >= 4-fold rise of hSBA titre from D0 before to D30 after the 12 to 18-month vaccination for Groups 1 and 2 - Per-Protocol Analysis Set 2

	Group 1 (N=560)			Group 2 (N=584)		
Serogroup	**n/M**	**%**	**95% CI**	**n/M**	**%**	**95% CI**
A	474/525	90.3	(87.4 ; 92.7)	497/553	89.9	(87.1 ; 92.3)
C	502/536	93.7	(91.2 ; 95.6)	518/567	91.4	(88.7 ; 93.5)
Y	482/539	89.4	(86.5 ; 91.9)	522/568	91.9	(89.3 ; 94.0)
W	492/531	92.7	(90.1 ; 94.7)	533/560	95.2	(93.1 ; 96.8)

n: number of subjects with valid serology results for the particular serogroup and who met the criterion.
M: number of subjects with valid serology results for the particular serogroup and time period.
N: number of subjects in per-protocol analysis set 2, for booster series.
Percentages are based on M.
95% CI of the single proportion calculated from the exact binomial method.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.

hSBA Seroresponse (Groups 1 and 2)

Table 47: Summary of hSBA vaccine seroresponse rate at D30 after the 4-month vaccination for Groups 1 and 2 - Per-Protocol Analysis Set 1

	Group 1 (N=522)			Group 2 (N=524)		
Serogroup	**n/M**	**%**	**95% CI**	**n/M**	**%**	**95% CI**
A	237/507	46.7	(42.3 ; 51.2)	307/504	60.9	(56.5 ; 65.2)
C	495/508	97.4	(95.7 ; 98.6)	446/514	86.8	(83.5 ; 89.6)
Y	447/513	87.1	(83.9 ; 89.9)	421/517	81.4	(77.8 ; 84.7)
W	478/516	92.6	(90.0 ; 94.7)	459/519	88.4	(85.4 ; 91.1)

n: Number of subjects who achieve the hSBA vaccine seroresponse.
M: number of subjects with valid serology results for the particular serogroup.
N: number of subjects in per-protocol analysis set 1, for primary series.
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.
95% CI of the single proportion calculated from the exact binomial method.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.

Table 48: Summary of hSBA vaccine seroresponse rate at D30 after the 12 to 18-month vaccination compared to D0 before the 2-month vaccination for Groups 1 and 2 - Per-Protocol Analysis Set 2

		Group 1 (N=560)			Group 2 (N=584)	
Serogroup	**n/M**	**%**	**95% CI**	**n/M**	**%**	**95% CI**
A	491/542	90.6	(87.8 ; 92.9)	517/564	91.7	(89.1 ; 93.8)
C	538/545	98.7	(97.4 ; 99.5)	523/573	91.3	(88.7 ; 93.5)
Y	544/551	98.7	(97.4 ; 99.5)	557/575	96.9	(95.1 ; 98.1)
W	542/545	99.4	(98.4 ; 99.9)	563/572	98.4	(97.0 ; 99.3)

n: Number of subjects who achieve the hSBA vaccine seroresponse.
M: number of subjects with valid serology results for the particular serogroup and time period.
N: number of subjects in per-protocol analysis set 2, for booster series.
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.
95% CI of the single proportion calculated from the exact binomial method.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix ® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.

Table 49: Summary of hSBA vaccine seroresponse rate at D30 compared to D0 before the 12 to 18-month vaccination for Groups 1 and 2 - Per-Protocol Analysis Set 2

		Group 1 (N=560)			Group 2 (N=584)	
Serogroup	**n/M**	**%**	**95% CI**	**n/M**	**%**	**95% CI**
A	465/525	88.6	(85.5 ; 91.2)	485/553	87.7	(84.7 ; 90.3)
C	502/536	93.7	(91.2 ; 95.6)	504/567	88.9	(86.0 ; 91.4)
Y	482/539	89.4	(86.5 ; 91.9)	512/568	90.1	(87.4 ; 92.5)
W	490/531	92.3	(89.7 ; 94.4)	530/560	94.6	(92.4 ; 96.4)

n: Number of subjects who achieve the hSBA vaccine seroresponse.
M: number of subjects with valid serology results for the particular serogroup and time period.
N: number of subjects in per-protocol analysis set 2, for booster series.
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.
95% CI of the single proportion calculated from the exact binomial method.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.

Secondary Objective #5: hSBA Antibody Responses Against the Meningococcal A, C, W, and Y Serogroups After a 4-dose Series of MenACYW Conjugate Vaccine (Group 4)

hSBA Antibody GMTs (Group 4)

Table 50: Summary of geometric means of hSBA titres at D0 before the 2-month vaccination and at D30 after the 6-month vaccination for Group 4 - Per-Protocol Analysis Set 1

			Group 4 (N=90)	
Serogroup	**Time Point**	**M**	**GMT**	**95% CI**
A	D0 before dose 1	89	2.86	(2.49 ; 3.28)
	D30 after dose 3	88	23.0	(17.1 ; 30.9)
C	D0 before dose 1	90	3.88	(3.25 ; 4.62)
	D30 after dose 3	90	481	(376 ; 616)
Y	D0 before dose 1	90	2.76	(2.36 ; 3.23)
	D30 after dose 3	90	150	(116 ; 195)
W	D0 before dose 1	90	3.08	(2.63 ; 3.60)
	D30 after dose 3	90	196	(156 ; 245)

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, for primary series.
95% CI calculated using calculation for normal distribution on log10(titer) following by antilog transformation.
Group 4: MenACYW conjugate vaccine administered at 2, 4, 6 and 12 to 18 months of age. Routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

Table 51: Summary of geometric means of hSBA titres at D0 before and at D30 after the 12 to 18-month vaccination for Group 4 - Per-Protocol Analysis Set 2

Serogroup	Time Point	M	Group 4 (N=90) GMT	95% CI
A	D0 before booster dose (Dose 4)	89	8.13	(6.33 ; 10.4)
	D30 after booster dose (Dose 4)	89	62.0	(39.9 ; 96.4)
C	D0 before booster dose (Dose 4)	89	56.9	(42.4 ; 76.4)
	D30 after booster dose (Dose 4)	86	791	(608 ; 1029)
Y	D0 before booster dose (Dose 4)	90	85.8	(68.2 ; 108)
	D30 after booster dose (Dose 4)	89	632	(512 ; 780)
W	D0 before booster dose (Dose 4)	90	92.6	(74.3 ; 115)
	D30 after booster dose (Dose 4)	86	1024	(806 ; 1301)

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, for booster series.
95% CI calculated using calculation for normal distribution on log10(titer) following by antilog transformation.
Group 4: MenACYW conjugate vaccine administered at 2, 4, 6 and 12 to 18 months of age. Routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

hSBA Antibody Titres >= 1:4 and >= 1:8 (Group 4)

In study MET58, immunogenicity of 3 primary doses administered at 2, 4, and 6 months of age was evaluated in a group of infants (N=90). Thirty days after the third dose was given at 6 months of age, the proportion of participants with an hSBA titre ≥1:8 were 81.8% (95% CI: 72.2; 89.2) for serogroup A and 98.9% (95% CI: 94.0; 100) for serogroups C, W, and Y, as per the below table.

Table 52: Distribution of hSBA titres at D0 before the 2-month vaccination and at D30 after the 6-month vaccination for Group 4 - Per-Protocol Analysis Set 1

Serogroup	Time Point	hSBA Titers	Group 4 (N=90) n/M	%
A	D0 before dose 1	<1:4	60/89	67.4
		>=1:4	29/89	32.6
		>=1:8	10/89	11.2
		>=1:16	4/89	4.5
		>=1:32	2/89	2.2
		>=1:64	1/89	1.1
	D30 after dose 3	<1:4	7/88	8.0
		>=1:4	81/88	92.0
		>=1:8	72/88	81.8
		>=1:16	61/88	69.3
		>=1:32	48/88	54.5
		>=1:64	25/88	28.4
		>=1:128	13/88	14.8
		>=1:256	6/88	6.8
		>=1:512	3/88	3.4
		>=1:1024	1/88	1.1
C	D0 before dose 1	<1:4	46/90	51.1
		>=1:4	44/90	48.9
		>=1:8	29/90	32.2
		>=1:16	7/90	7.8
		>=1:32	4/90	4.4
		>=1:64	2/90	2.2
	D30 after dose 3	<1:4	1/90	1.1
		>=1:4	89/90	98.9
		>=1:8	89/90	98.9
		>=1:16	89/90	98.9
		>=1:32	86/90	95.6
		>=1:64	86/90	95.6
		>=1:128	83/90	92.2
		>=1:256	78/90	86.7
		>=1:512	68/90	75.6
		>=1:1024	37/90	41.1
		>=1:2048	5/90	5.6
		>=1:4096	2/90	2.2
Y	D0 before dose 1	<1:4	70/90	77.8
		>=1:4	20/90	22.2
		>=1:8	11/90	12.2
		>=1:16	6/90	6.7
		>=1:32	3/90	3.3
		>=1:64	1/90	1.1
		>=1:128	1/90	1.1
	D30 after dose 3	<1:4	1/90	1.1

		>=1:4	89/90	98.9
		>=1:8	89/90	98.9
		>=1:16	87/90	96.7
		>=1:32	85/90	94.4
		>=1:64	76/90	84.4
		>=1:128	60/90	66.7
		>=1:256	42/90	46.7
		>=1:512	26/90	28.9
		>=1:1024	7/90	7.8
W	D0 before dose 1	<1:4	58/90	64.4
		>=1:4	32/90	35.6
		>=1:8	15/90	16.7
		>=1:16	4/90	4.4
		>=1:32	2/90	2.2
		>=1:64	2/90	2.2
		>=1:128	1/90	1.1
	D30 after dose 3	<1:4	1/90	1.1
		>=1:4	89/90	98.9
		>=1:8	89/90	98.9
		>=1:16	89/90	98.9
		>=1:32	86/90	95.6
		>=1:64	84/90	93.3
		>=1:128	71/90	78.9
		>=1:256	56/90	62.2
		>=1:512	24/90	26.7
		>=1:1024	7/90	7.8

n: number of subjects experiencing the endpoint listed in the first 3 columns
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, for primary series.
Percentages are based on M.
Group 4: MenACYW conjugate vaccine administered at 2, 4, 6 and 12 to 18 months of age. Routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

In the PPAS2, the percentages of subjects in Group 4 with hSBA titres ≥ 1:4 and ≥ 1:8 remained high from D0 pre-dose 4 to D30 post-dose 4 of MenACYW conjugate vaccine (booster dose at 12 to 18 months of age) for serogroups C, Y, and W. For serogroup A, the percentage from D0 pre-dose 4 to D30 post-dose 4 remained high for subjects with hSBA titres ≥ 1:4 and increased for subjects with hSBA titres ≥ 1:8. The percentages from pre- to post-vaccination were:

- For serogroup A: from 80.9% to 82.0% for hSBA titres ≥ 1:4 and from 52.8% (95% CI: 41.9;63.5) to 82.0% (95% CI: 72.5;89.4) for hSBA titres ≥ 1:8
- For serogroup C: from 97.8% to 100% for hSBA titres ≥ 1:4 and from 92.1% (95% CI: 84.5;96.8) to 100% (95% CI: 95.8;100) for hSBA titres ≥ 1:8
- For serogroups Y and W: 100% at pre- and post-vaccination for hSBA titres ≥ 1:4 and ≥ 1:8 (100% (95% CI: 96.0;100) to 100% (95% CI: 95.8;100) for serogroup W, and 100% (95% CI: 96.0;100) to 100% (95% CI: 95.9;100) for serogroup Y).

hSBA Seroresponse (Group 4)

Table 53: Summary of hSBA vaccine seroresponse rate at D30 after the 6-month vaccination for Group 4 - Per-Protocol Analysis Set 1

		Group 4 (N=90)	
Serogroup	n/M	%	95% CI
A	57/87	65.5	(54.6 ; 75.4)
C	87/90	96.7	(90.6 ; 99.3)
Y	85/90	94.4	(87.5 ; 98.2)
W	86/90	95.6	(89.0 ; 98.8)

n: Number of subjects who achieve the hSBA vaccine seroresponse.
M: number of subjects with valid serology results for the particular serogroup.
N: number of subjects in per-protocol analysis set 1, for primary series.
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.
95% CI of the single proportion calculated from the exact binomial method.
Group 4: MenACYW conjugate vaccine administered at 2, 4, 6 and 12 to 18 months of age. Routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

Table 54: Summary of hSBA vaccine seroresponse rate at D30 after the 12 to 18-month vaccination compared to D0 before the 2-month vaccination for Group 4 - Per-Protocol Analysis Set 2

Serogroup	n/M	Group 4 (N=90) %	95% CI
A	65/88	73.9	(63.4 ; 82.7)
C	85/86	98.8	(93.7 ; 100)
Y	88/89	98.9	(93.9 ; 100)
W	85/86	98.8	(93.7 ; 100)

n: number of subjects who achieve the hSBA vaccine seroresponse.
M: number of subjects with valid serology results for the particular serogroup and time period.
N: number of subjects in per-protocol analysis set 2, for booster series.
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.
95% CI of the single proportion calculated from the exact binomial method.
Group 4: MenACYW conjugate vaccine administered at 2, 4, 6 and 12 to 18 months of age. Routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

Table 55: Summary of hSBA vaccine seroresponse rate at D30 compared to D0 before the 12 to 18-month vaccination for Group 4 - Per-Protocol Analysis Set 2

Serogroup	n/M	Group 4 (N=90) %	95% CI
A	56/88	63.6	(52.7 ; 73.6)
C	82/86	95.3	(88.5 ; 98.7)
Y	72/89	80.9	(71.2 ; 88.5)
W	77/86	89.5	(81.1 ; 95.1)

n: number of subjects who achieve the hSBA vaccine seroresponse.
M: number of subjects with valid serology results for the particular serogroup and time period.
N: number of subjects in per-protocol analysis set 2, for booster series.
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.
95% CI of the single proportion calculated from the exact binomial method.
Group 4: MenACYW conjugate vaccine administered at 2, 4, 6 and 12 to 18 months of age. Routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

Secondary Objective #6: Antibody Responses Against the Antigens of the Concomitant Routine Vaccines After a 4-dose Series of MenACYW Conjugate Vaccine (Group 4)

Anti-tetanus antibodies, anti-diphtheria antibodies, anti-poliovirus antibodies (types 1, 2, and 3), anti-PRP antibodies, anti-HBsAg antibody concentration, anti-pertussis antibody concentration (PT and FHA)

Table 56: Summary of geometric means of hexavalent vaccine before and at D30 after the 12 to 18-month vaccination for Group 4 - Per-Protocol Analysis Set 2

Antigens	Time Point	M	Group 4 (N=90) GM	95% CI
Anti-tetanus	D0 before booster dose (Dose 4)	90	0.381	(0.311 ; 0.466)
	D30 after booster dose (Dose 4)	89	7.00	(5.99 ; 8.18)
Anti-diphtheria	D0 before booster dose (Dose 4)	89	0.101	(0.082 ; 0.124)
	D30 after booster dose (Dose 4)	89	3.26	(2.88 ; 3.69)
Anti-polio 1	D0 before booster dose (Dose 4)	88	63.3	(44.9 ; 89.2)
	D30 after booster dose (Dose 4)	87	1625	(1291 ; 2047)
Anti-polio 2	D0 before booster dose (Dose 4)	88	110	(76.9 ; 158)
	D30 after booster dose (Dose 4)	87	3858	(3001 ; 4960)
Anti-polio 3	D0 before booster dose (Dose 4)	88	34.9	(24.4 ; 49.9)
	D30 after booster dose (Dose 4)	87	3397	(2567 ; 4495)
Anti-PRP	D0 before booster dose (Dose 4)	90	0.251	(0.188 ; 0.336)
	D30 after booster dose (Dose 4)	90	16.1	(12.1 ; 21.6)
Anti-HBsAg	D0 before booster dose (Dose 4)	90	22.8	(15.4 ; 33.7)
	D30 after booster dose (Dose 4)	86	1144	(648 ; 2020)
Anti-PT	D0 before booster dose (Dose 4)	90	10.7	(8.82 ; 13.1)
	D30 after booster dose (Dose 4)	89	80.9	(68.2 ; 95.9)
Anti-FHA	D0 before booster dose (Dose 4)	90	30.3	(25.0 ; 36.7)
	D30 after booster dose (Dose 4)	89	181	(151 ; 217)

M: Number of subjects with available data for the endpoint.
N: number of subjects in per-protocol analysis set 2, for booster series.
95% CI calculated using calculation for normal distribution on log10(titer) following by antilog transformation.
Group 4: MenACYW conjugate vaccine administered at 2, 4, 6 and 12 to 18 months of age. Routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

Table 57: Summary of response rate of hexavalent vaccine before and at D30 after the 12 to 18-month vaccination for Group 4 - Per-Protocol Analysis Set 2

			Group 4 (N=90)		
Antigens	**Criterion**	**Time Point**	**n/M**	**%**	**95% CI**
Anti-tetanus	>=0.01 IU/mL	D0 before booster dose (Dose 4)	90/90	100	(96.0 ; 100)
		D30 after booster dose (Dose 4)	89/89	100	(95.9 ; 100)
	>=0.1 IU/mL	D0 before booster dose (Dose 4)	83/90	92.2	(84.6 ; 96.8)
		D30 after booster dose (Dose 4)	89/89	100	(95.9 ; 100)
	>=1.0 IU/mL	D0 before booster dose (Dose 4)	14/90	15.6	(8.8 ; 24.7)
		D30 after booster dose (Dose 4)	88/89	98.9	(93.9 ; 100)
Anti-diphtheria	>=0.01 IU/mL	D0 before booster dose (Dose 4)	88/89	98.9	(93.9 ; 100)
		D30 after booster dose (Dose 4)	89/89	100	(95.9 ; 100)
	>=0.1 IU/mL	D0 before booster dose (Dose 4)	38/89	42.7	(32.3 ; 53.6)
		D30 after booster dose (Dose 4)	89/89	100	(95.9 ; 100)
	>=1.0 IU/mL	D0 before booster dose (Dose 4)	0/89	0	(0 ; 4.1)
		D30 after booster dose (Dose 4)	89/89	100	(95.9 ; 100)
Anti-polio 1	>=1:8	D0 before booster dose (Dose 4)	80/88	90.9	(82.9 ; 96.0)
		D30 after booster dose (Dose 4)	87/87	100	(95.8 ; 100)
Anti-polio 2	>=1:8	D0 before booster dose (Dose 4)	80/88	90.9	(82.9 ; 96.0)
		D30 after booster dose (Dose 4)	87/87	100	(95.8 ; 100)
Anti-polio 3	>=1:8	D0 before booster dose (Dose 4)	65/88	73.9	(63.4 ; 82.7)
		D30 after booster dose (Dose 4)	87/87	100	(95.8 ; 100)
Anti-PRP	>=0.15 ug/mL	D0 before booster dose (Dose 4)	60/90	66.7	(55.9 ; 76.3)
		D30 after booster dose (Dose 4)	90/90	100	(96.0 ; 100)
	>=1 ug/mL	D0 before booster dose (Dose 4)	11/90	12.2	(6.3 ; 20.8)
		D30 after booster dose (Dose 4)	87/90	96.7	(90.6 ; 99.3)
Anti-HBsAg	>=10 mIU/mL	D0 before booster dose (Dose 4)	58/90	64.4	(53.7 ; 74.3)
		D30 after booster dose (Dose 4)	79/86	91.9	(83.9 ; 96.7)
	>=100 mIU/mL	D0 before booster dose (Dose 4)	25/90	27.8	(18.9 ; 38.2)
		D30 after booster dose (Dose 4)	72/86	83.7	(74.2 ; 90.8)

n: Number of subjects that met the criterion
M: Number of subjects with available data for the endpoint. Percentages are based on M.
N: number of subjects in per-protocol analysis set 2, for booster series.
95% CI of the single proportion calculated from the exact binomial method.
Group 4: MenACYW conjugate vaccine administered at 2, 4, 6 and 12 to 18 months of age. Routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

Anti-pertussis antibody concentration (PT and FHA)

Table 58: Summary of Pertussis vaccine seroresponse rate for anti-PT and anti-FHA at D30 after the 12 to 18-month vaccination for Group 4 - Per-Protocol Analysis Set 2

		Group 4 (N=90)	
Antigens	**n/M**	**%**	**95% CI**
Anti-PT	79/89	88.8	(80.3 ; 94.5)
Anti-FHA	81/89	91.0	(83.1 ; 96.0)

n: number of subjects with valid serology results for the particular antigen and who met the criterion.
M: Number of subjects with available data for the endpoint.
N: number of subjects in per-protocol analysis set 2, for booster series.
Pertussis vaccine seroresponse for anti-PT and anti-FHA is defined as: for a subject with a pre-booster vaccination concentration < 4 x lower level of quantitation (LLOQ), post-booster vaccination concentration must be >= 4 x LLOQ; for a subject with a pre-booster vaccination concentration >= 4 x LLOQ, post-booster vaccination concentration must be >= 2x pre-booster vaccination concentration.
Group 4: MenACYW conjugate vaccine administered at 2, 4, 6 and 12 to 18 months of age. Routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

Anti-pneumococcal antibody concentration against the antigens of PCV13

Table 59: Summary of geometric means of PCV13 vaccine at D30 after the 12 to 18-month vaccination for Group 4 - Per-Protocol Analysis Set 2

Serotype	M	Group 4 (N=90) GMC	95% CI
1	89	5.47	(4.66 ; 6.42)
3	89	1.21	(0.982 ; 1.50)
4	89	3.97	(3.35 ; 4.70)
5	89	3.95	(3.36 ; 4.65)
6A	89	14.3	(12.2 ; 16.8)
6B	89	9.41	(7.86 ; 11.3)
7F	89	4.92	(4.20 ; 5.76)
9V	89	5.40	(4.65 ; 6.26)
14	89	14.7	(12.1 ; 17.9)
18C	89	3.48	(3.00 ; 4.03)
19A	89	10.9	(9.26 ; 12.9)
19F	89	12.2	(10.5 ; 14.2)
23F	89	4.06	(3.45 ; 4.76)

M: Number of subjects with available data for the endpoint.
N: number of subjects in per-protocol analysis set 2, for booster series.
95% CI calculated using calculation for normal distribution on log10(titer) following by antilog transformation.
Group 4: MenACYW conjugate vaccine administered at 2, 4, 6 and 12 to 18 months of age. Routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

Table 60: Summary of response rate of PCV13 vaccine at D30 after the 12 to 18-month vaccination for Group 4 - Per-Protocol Analysis Set 2

Serotype	Criterion	n/M	Group 4 (N=90) %	95% CI
1	>=0.35 ug/mL	89/89	100	(95.9 ; 100)
	>=1 ug/mL	88/89	98.9	(93.9 ; 100)
3	>=0.35 ug/mL	82/89	92.1	(84.5 ; 96.8)
	>=1 ug/mL	47/89	52.8	(41.9 ; 63.5)
4	>=0.35 ug/mL	89/89	100	(95.9 ; 100)
	>=1 ug/mL	86/89	96.6	(90.5 ; 99.3)
5	>=0.35 ug/mL	89/89	100	(95.9 ; 100)
	>=1 ug/mL	86/89	96.6	(90.5 ; 99.3)
6A	>=0.35 ug/mL	89/89	100	(95.9 ; 100)
	>=1 ug/mL	88/89	98.9	(93.9 ; 100)
6B	>=0.35 ug/mL	89/89	100	(95.9 ; 100)
	>=1 ug/mL	89/89	100	(95.9 ; 100)
7F	>=0.35 ug/mL	89/89	100	(95.9 ; 100)
	>=1 ug/mL	88/89	98.9	(93.9 ; 100)
9V	>=0.35 ug/mL	89/89	100	(95.9 ; 100)
	>=1 ug/mL	88/89	98.9	(93.9 ; 100)
14	>=0.35 ug/mL	89/89	100	(95.9 ; 100)
	>=1 ug/mL	89/89	100	(95.9 ; 100)
18C	>=0.35 ug/mL	89/89	100	(95.9 ; 100)
	>=1 ug/mL	87/89	97.8	(92.1 ; 99.7)
19A	>=0.35 ug/mL	89/89	100	(95.9 ; 100)
	>=1 ug/mL	89/89	100	(95.9 ; 100)
19F	>=0.35 ug/mL	89/89	100	(95.9 ; 100)
	>=1 ug/mL	89/89	100	(95.9 ; 100)
23F	>=0.35 ug/mL	89/89	100	(95.9 ; 100)
	>=1 ug/mL	88/89	98.9	(93.9 ; 100)

n: Number of subjects that met the criterion.
M: Number of subjects with available data for the endpoint. Percentages are based on M.
N: number of subjects in per-protocol analysis set 2, for booster series.
95% CI of the single proportion calculated from the exact binomial method.
Group 4: MenACYW conjugate vaccine administered at 2, 4, 6 and 12 to 18 months of age. Routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

Anti-measles, anti-mumps, and anti-rubella antibody concentration

Table 61: Summary of response rate of MMR vaccine at D30 after the 12 to 18-month vaccination for Group 4 - Per-Protocol Analysis Set 2

Antigens	Serostatus cutoff	n/M	Group 4 (N=90) %	95% CI
Anti-measles	>=255 mIU/mL	88/90	97.8	(92.2 ; 99.7)
Anti-mumps	>=10 Mumps Ab units/mL	90/90	100	(96.0 ; 100)
Anti-rubella	>=10 IU/mL	90/90	100	(96.0 ; 100)

n: Number of subjects that met the criterion.
M: Number of subjects with available data for the endpoint when the MMR vaccine has been administered concomitantly with the study vaccines. Percentages are based on M.
N: number of subjects in per-protocol analysis set 2, for booster series.
95% CI of the single proportion calculated from the exact binomial method.
Group 4: MenACYW conjugate vaccine administered at 2, 4, 6 and 12 to 18 months of age. Routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.

For results of Observational Immunogenicity Objective: rSBA Antibody Responses Against the Meningococcal A, C, W, and Y Serogroups After Vaccination With MenACYW Conjugate Vaccine or Nimenrix (All Groups) and rSBA Antibody Titres, it is referred to the CSR of Study MET58.

Ancillary analyses

Post-hoc Analysis Results (MET58)

Table 62: Non-inferiority of the hSBA vaccine seroresponse rate at D30 after the 12 to 18-month vaccination compared to D0 before the 2-month vaccination for Group 1 versus 2 - Per-Protocol Analysis Set 2

	Group 1 (N=560)			Group 2 (N=584)			Group 1 - Group 2		
Serogroup	n/M	%	95% CI	n/M	%	95% CI	Difference (%)	95% CI	Non-inferiority
A	491/542	90.6	(87.8 ; 92.9)	517/564	91.7	(89.1 ; 93.8)	-1.08	(-4.48 ; 2.30)	Yes
C	538/545	98.7	(97.4 ; 99.5)	523/573	91.3	(88.7 ; 93.5)	7.44	(5.00 ; 10.12)	Yes
Y	544/551	98.7	(97.4 ; 99.5)	557/575	96.9	(95.1 ; 98.1)	1.86	(0.11 ; 3.74)	Yes
W	542/545	99.4	(98.4 ; 99.9)	563/572	98.4	(97.0 ; 99.3)	1.02	(-0.27 ; 2.46)	Yes

n: number of subjects who achieve the hSBA vaccine seroresponse.
M: number of subjects with valid serology results for the particular serogroup and time period. N: number of subjects in per-protocol analysis set 2, for booster series.
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
95% CI of the single proportion calculated from the exact binomial method. 95% CI of the difference calculated from the Wilson Score method without continuity correction.
The overall non-inferiority will be demonstrated if the lower limit of the 2-sided 95% CI is > -10% for all four serogroups.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.

Subgroup Analysis by Gender (MET58)

Table 63: hSBA vaccine antibody titres at D30 after a 3-dose series vaccination for Group 1 versus 2 by gender - Per-Protocol Analysis Set 2

		Group 1 (N=560)			Group 2 (N=584)			Group 1/Group 2	
Gender	Serogroup	M	GMT	95% CI	M	GMT	95% CI	Ratio	95% CI
Female	A	272	117	(96.0 ; 143)	296	192	(159 ; 232)	0.612	(0.465 ; 0.805)
	C	276	529	(454 ; 616)	302	123	(105 ; 145)	4.29	(3.43 ; 5.36)
	Y	279	279	(245 ; 318)	302	171	(149 ; 197)	1.63	(1.35 ; 1.97)
	W	274	439	(382 ; 504)	298	284	(247 ; 326)	1.55	(1.27 ; 1.88)
Male	A	271	145	(119 ; 178)	271	186	(152 ; 229)	0.780	(0.584 ; 1.04)
	C	274	604	(513 ; 711)	276	115	(95.8 ; 139)	5.23	(4.08 ; 6.69)
	Y	275	291	(254 ; 334)	277	148	(128 ; 172)	1.96	(1.61 ; 2.40)
	W	273	407	(351 ; 472)	277	265	(227 ; 310)	1.54	(1.24 ; 1.90)

n: Number of subjects with available hSBA antibody titers values. M: Number of subjects with available data for the endpoint.
N: number of subjects in per-protocol analysis set 2, for booster series.
95% CI of the GM calculated on Log10 titers using the usual calculation for normal distribution, then antilog transformations will be applied to the results of calculations.
95% CI of the ratio calculated using a normal approximation of log-transformed titers.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.

Table 64: Percentage of subjects with hSBA antibody titres >=1:8 at D30 after Dose 2 for Group 1 versus 2 by gender - Per-Protocol Analysis Set 1

		Group 1 (N=522)			Group 2 (N=524)			Group 1 - Group 2	
Gender	Serogroup	n/M	%	95% CI	n/M	%	95% CI	Difference (%)	95% CI
Female	A	175/267	65.5	(59.5 ; 71.2)	191/254	75.2	(69.4 ; 80.4)	-9.65	(-17.32 ; -1.80)
	C	264/268	98.5	(96.2 ; 99.6)	243/264	92.0	(88.1 ; 95.0)	6.46	(2.93 ; 10.47)
	Y	263/270	97.4	(94.7 ; 99.0)	252/266	94.7	(91.3 ; 97.1)	2.67	(-0.72 ; 6.30)
	W	263/271	97.0	(94.3 ; 98.7)	254/266	95.5	(92.3 ; 97.6)	1.56	(-1.80 ; 5.08)
Male	A	148/241	61.4	(54.9 ; 67.6)	194/254	76.4	(70.7 ; 81.5)	-14.97	(-22.87 ; -6.82)
	C	243/245	99.2	(97.1 ; 99.9)	236/257	91.8	(87.8 ; 94.9)	7.35	(3.88 ; 11.40)
	Y	235/246	95.5	(92.1 ; 97.7)	237/257	92.2	(88.2 ; 95.2)	3.31	(-0.99 ; 7.70)
	W	237/247	96.0	(92.7 ; 98.0)	240/257	93.4	(89.6 ; 96.1)	2.57	(-1.49 ; 6.72)

n: Number of subjects with available hSBA antibody titers values. M: Number of subjects with available data for the endpoint.
N: number of subjects in per-protocol analysis set 1, for primary series
95% CI of the single proportion calculated from the exact binomial method.
95% CI of the difference calculated from the Wilson Score method without continuity correction.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.

Subgroup Analysis by Age Group (MET58)

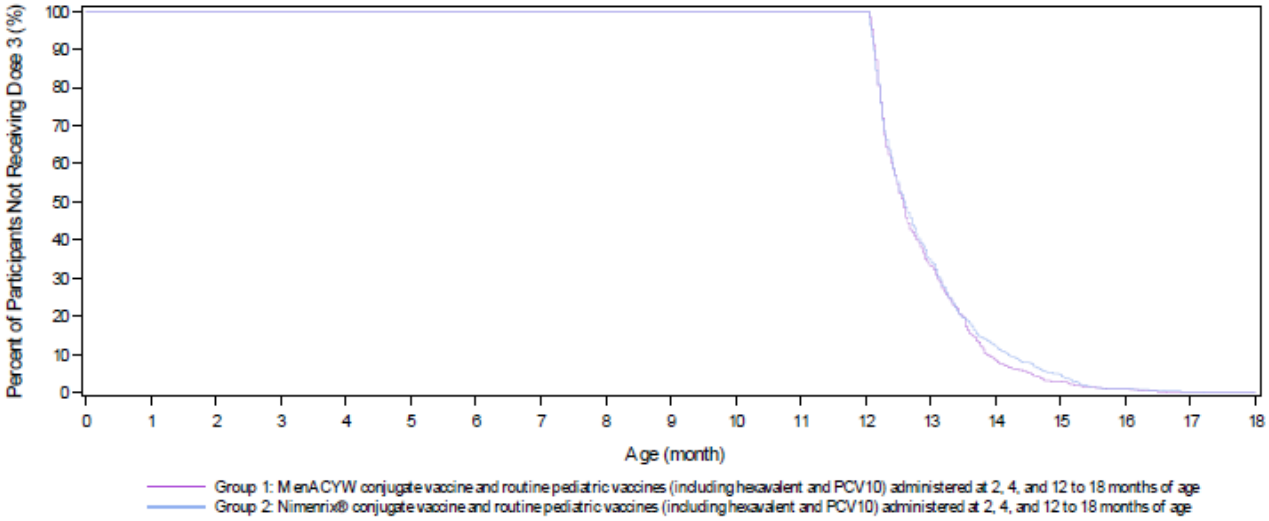
Table 65: hSBA vaccine antibody titres at D30 after a 3-dose series vaccination for Group 1 versus 2 by age group - Per-Protocol Analysis Set 2

		Group 1 (N=560)			Group 2 (N=584)			Group 1/Group 2	
Age group	Serogroup	M	GMT	95% CI	M	GMT	95% CI	Ratio	95% CI
42-59 days	A	83	98.0	(65.3 ; 147)	93	145	(99.4 ; 212)	0.674	(0.389 ; 1.17)
	C	85	355	(270 ; 465)	94	93.9	(65.9 ; 134)	3.78	(2.42 ; 5.89)
	Y	87	262	(201 ; 342)	94	149	(114 ; 195)	1.75	(1.20 ; 2.56)
	W	84	445	(330 ; 600)	93	332	(258 ; 428)	1.34	(0.909 ; 1.97)
60-89 days	A	460	138	(118 ; 160)	474	199	(172 ; 231)	0.690	(0.558 ; 0.854)
	C	465	615	(545 ; 694)	484	125	(110 ; 143)	4.91	(4.11 ; 5.86)
	Y	467	290	(262 ; 320)	485	162	(145 ; 181)	1.79	(1.54 ; 2.07)
	W	463	419	(377 ; 466)	482	265	(236 ; 297)	1.58	(1.35 ; 1.85)

n: Number of subjects with available hSBA antibody titers values. M: Number of subjects with available data for the endpoint.
N: number of subjects in per-protocol analysis set 2, for booster series.
95% CI of the GM calculated on Log10 titers using the usual calculation for normal distribution, then antilog transformations will be applied to the results of calculations.
95% CI of the ratio calculated using a normal approximation of log-transformed titers.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.

Analysis of participants' age (month) at 3rd (booster) dose (MET58)

Table 66: Kaplan-Meier curve of time from birth to the time of receiving Dose 3 for study groups 1 and 2 - PPAS2, MET 58



Supportive studies

The results of the supportive studies below are focused on their usability in adding on immunogenicity aspects of Study MET58, for instance on concomitant vaccination. For other data it is referred to their respective procedures or CSRs.

MET33

Methods

Study MET33 was 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** [Meningococcal {Groups A, C, Y and W-135} Oligosaccharide Diphtheria CRM197 Conjugate Vaccine]) when administered concomitantly with routine paediatric vaccines (Prevnar 13, Hexacima, RotaTeq, and M-M-R II) 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.

A total of 525 subjects were 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 into the following groups:

Mexico

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

The Russian Federation

- **Group 3**: **MenACYW conjugate vaccine** at 3, 6, and 12 months of age + routine paediatric vaccines at 2, 3, 4.5, 6, and 12 months of age
- **Group 4:** Routine paediatric vaccines at 2, 3, 4.5, 6, and 12 months of age

Table 67: Schedule of vaccination and blood draws – MET33 (Mexico)

Visit (V)	V01	V02	V03	V04	V05	V06[+]
Individual 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**

BL: Blood sample; V: Visit

[+]Per the current National Immunization Program 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 will be measured for this vaccine, even if it was administered at V6 of the study.

[†]MenACYW conjugate vaccine

Table 68: Schedule of vaccination, blood draws, and urinalysis – MET33 (Russian Federation)

Visit (V)	V0	V01	V02	V03	V04	V05	V06	V07
Individual 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)

BL: Blood sample 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 not provided by the Sponsor but procured by the sites as per their standard practices.
‡The 4th dose of Pentaxim®, which is administered at 18 months of age, was considered out of the scope of the study, and it was not be provided by the Sponsor but procured by the sites as per their standard practices. Individuals were instructed to receive it for completion of the Pentavalent series as per the NIC of the Russian Federation recommendation.
§In the event ENGERIX-B® cannot be supplied in the Russian Federation, a locally licensed monovalent hepatitis B vaccine was administered instead. Further details provided in 5.3.5.1 MET33 CSR.
**In the event M-M-R®II combination vaccine cannot be supplied or was unavailable in the Russian Federation, locally licensed MMR or MM+R vaccines were administered instead. Further details provided in 5.3.5.1 MET33 CSR

Results

Primary Immunogenicity Objective

Table 69: Number and percentage of subjects with hSBA titre ⩾ 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)

Rotavirus

Table 70: 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 71: Summary of geometric means 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**	**M**	**Geometric mean**	**(95% CI)**	**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)

MET52

Methods

Study MET52 was a Phase III, open-label, randomised, parallel-group, active-controlled, multi-centre study to evaluate the immunogenicity and describe the safety of **MenACYW conjugate vaccine** when administered concomitantly with a **Meningococcal Group B vaccine** and other routine paediatric vaccines as part of the National Immunisation Schedule in healthy infants and toddlers in the United Kingdom.

Approximately 800 healthy infants aged ≥ 56 to ≤ 89 days (approximately 2 months of age) were to be randomised 2:2:1 to the following 3 groups:

- **Group 1: MenACYW conjugate vaccine** at 3 months and at 12 to 13 months of age; Bexsero at 2, 4, and 12 to 13 months of age
- **Group 2: MenACYW conjugate vaccine** at 3 months and at 12 to 13 months of age; Bexsero at 2 and 4 months of age (this group received their 3rd dose of Bexsero following completing of study procedures as described below)
- **Group 3: Bexsero** at 2, 4, and 12 to 13 months of age

Table 72: Schedule of vaccination and blood draws – MET52

	Visit								
	Visit 1 2 months of age	Visit 2 3 months of age		Visit 3 4 months of age		Visit 4 12 to 13 months of age		Visit 5 13 to 14 months of age	
Group	Vaccinations	Blood collection	Vaccinations	Blood collection	Vaccinations	Blood collection	Vaccination(s)	Blood collection	Vaccinations*
1 (N=320)	Infanrix hexa Rotarix Bexsero PCV13	BL1 (n=70)†	Infanrix hexa Rotarix MenACYW	BL2 (n=70)† BL1 (n=90)‡	Infanrix hexa Bexsero PCV13	BL2 (n=90)‡	Bexsero MenACYW	BL3 (n=320)	PCV13 Menitorix Priorix/M-M-RVAXPRO
2 (N=320)	Infanrix hexa Rotarix Bexsero PCV13	BL1 (n=70)†	Infanrix hexa Rotarix MenACYW	BL2 (n=70)† BL1 (n=90)‡	Infanrix hexa Bexsero PCV13	BL2 (n=90)‡	MenACYW	BL3 (n=320)	PCV13 Menitorix Bexsero§ Priorix/M-M-RVAXPRO
3** (N=160)	Infanrix hexa Rotarix Bexsero PCV13	BL1 (n=70)†	Infanrix hexa Rotarix	BL2 (n=70)† BL1 (n=90)‡	Infanrix hexa Bexsero PCV13	BL2 (n=90)‡	Bexsero	BL3 (n=160)	PCV13 Menitorix Priorix/M-M-RVAXPRO

*Routine vaccines given after study visit procedures were completed. No immunogenicity or safety data were collected after the administration of these vaccines
†The first ~70 individuals randomized to have 2 blood draws at Visit 2 and Visit 3 (Subset A)
‡The last ~90 individuals randomized to have 2 blood draws at Visit 3 and Visit 4 (Subset B)
§For Group 2, the 3rd dose of Bexsero was provided by Sponsor for completion of the Bexsero vaccination series
**Licensed ACWY conjugate meningococcal vaccine (Nimenrix) was offered at least 30 days after the last study visit (Visit 5) at an additional optional visit
BL: Blood draw prior to vaccination; N: number of individuals randomized in each group; n: number of individuals randomized to have blood draws in each group at the given visit

Results

Primary Immunogenicity Objective

Table 73: Non-inferiority of hSBA vaccine seroprotection (titre >= 1:8) at D30 after the 2nd MenACYW vaccination (12 through 13 months of age) for Group 1 versus Group 2 - Per-Protocol Analysis Set 3

	Group 1 (N=178)			Group 2 (N=169)			Group 1 minus Group 2		
Serogroup	n/M	%	(95% CI)	n/M	%	(95% CI)	Difference (%)	(95% CI)	Non-inferiority
A	159/159	100	(97.7 ; 100)	155/156	99.4	(96.5 ; 100)	0.64	(-1.78 ; 3.54)	Yes
C	168/168	100	(97.8 ; 100)	165/165	100	(97.8 ; 100)	0.00	(-2.24 ; 2.28)	Yes
Y	161/161	100	(97.7 ; 100)	159/159	100	(97.7 ; 100)	0.00	(-2.33 ; 2.36)	Yes
W	171/172	99.4	(96.8 ; 100)	160/160	100	(97.7 ; 100)	-0.58	(-3.22 ; 1.81)	Yes

n: number of subjects who achieve an hSBA vaccine seroprotection; M: number of subjects with available data for the relevant endpoint.
N: number of subjects in per-protocol analysis set for second year of life vaccination
95% CI of the single proportion calculated from the exact binomial method;
95% CI of the difference calculated from the Wilson Score method without continuity correction
The overall non-inferiority will be demonstrated if the lower limit of the 2-sided 95% CI is > -10% for all four serogroups.
Group 1: MenACYW conjugate vaccine at 3 months and at 12 to 13 months of age; Bexsero at 2, 4, and 12 to 13 months of age
Group 2: MenACYW conjugate vaccine at 3 months and at 12 to 13 months of age; Bexsero at 2 and 4 months of age

MET42

Methods

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

Approximately 2628 healthy infants aged ≥ 42 to ≤ 89 days were planned to be randomised 2:1 to the following 2 groups.

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

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

Group 1:

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

Group 2:

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

Table 74: Vaccination and blood sampling schedule – MET42

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

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

Results

Primary Immunogenicity Objective

Table 75: Co-primary objective #1: Non-inferiority of hSBA vaccine seroresponse rate at D30 after the 4th dose - Per-Protocol Analysis Set 3

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

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

Table 76: Co-primary objective #2: Non-inferiority of the percentage of subjects with hSBA antibody titres >=1:8 at D30 after the 3rd dose - Per-Protocol Analysis Set 1

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

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

Rotavirus

Table 77: Non-inferiority of the percentage of subjects with anti-rotavirus IgA antibody concentrations >= 3-fold rise at D30 after the 6-month vaccinations - Per-Protocol Analysis Set 1

	Group 1 (N=928)			Group 2 (N=460)			Group 1 - Group 2		
Antigen	n/M	%	95% CI	n/M	%	95% CI	Difference (%)	95% CI	Non-inferiority
Anti-rotavirus	603/663	91.0	(88.5 ; 93.0)	298/321	92.8	(89.4 ; 95.4)	-1.88	(-5.26 ; 2.00)	Yes

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

Table 78: Non-inferiority of geometric mean concentrations (GMCs) of anti-rotavirus IgA antibody at D30 after the 6-month vaccinations - Per-Protocol Analysis Set 1

	Group 1 (N=928)			Group 2 (N=460)			Group 1 / Group 2		
Antigen	M	GMC	95% CI	M	GMC	95% CI	GMC Ratio	95% CI	Non-inferiority
Anti-rotavirus	857	272	(244 ; 303)	403	308	(264 ; 360)	0.881	(0.728 ; 1.07)	Yes

M: Number of subjects with available data for the endpoint.
N: number of subjects in per-protocol analysis set 1, for infant vaccinations
95% CI calculated using calculation for normal distribution on log10(concentration) following by antilog transformation
Non-inferiority will be demonstrated if the lower limit of the 2-sided 95% CI is > 2/3
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines
Group 2: MENVEO® and routine pediatric vaccines

Varicella zoster virus (VZV/HHV-3)

Table 79: Non-inferiority of VARIVAX vaccine response rates at D30 after the 12-month vaccinations - Per-protocol Analysis Set 3

		Group 1a (N=675)			Group 2a (N=308)			Group 1a - Group 2a		
Antigen	Criterion	n/M	%	95% CI	n/M	%	95% CI	Difference (%)	95% CI	Non-inferiority
Anti-varicella	>=5 gpELISA units/mL	638/662	96.4	(94.7 ; 97.7)	285/301	94.7	(91.5 ; 96.9)	1.69	(-0.96 ; 5.05)	Yes

n: Number of subjects with specific antibody concentrations that met the corresponding criterion
M: Number of subjects with available data for the endpoint.
N: number of subjects in full analysis set 3, for 2nd year of life vaccinations
95% CI of the single proportion calculated from the exact binomial method.
95% CI of the difference calculated from the Wilson Score method without continuity correction
Non-inferiority will be demonstrated if the lower limit of the 2-sided 95% CI is > -10%
Group 1a: MenACYW conjugate vaccine and routine vaccines at 2, 4, 6, and 12 to 15 months of age
Group 2a: MENVEO® at 2, 4, 6, and 12 months of age and routine vaccines at 2, 4, 6, 12, and 15 to 18 months of age

MET61

Methods

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

Approximately 1070 subjects were to be enrolled. Approximately 870 healthy infants 6 to 7 months of age were to be randomised 1:1 to 2 groups, and 200 healthy toddlers 17 to 19 months of age were to be randomised 1:1 to 2 groups:

- **Group 1: MenACYW conjugate vaccine** + routine paediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
- **Group 2: MENVEO** + routine paediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
- **Group 3: MenACYW conjugate vaccine** at 17 to 19 months of age and 20 to 23 months of age
- **Group 4: Menactra** at 17 to 19 months of age and 20 to 23 months of age

Table 80: Vaccination and blood sampling schedule - Group 1 and Group 2 – MET61 (according to protocol)

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

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

Table 81: Vaccination and blood sampling schedule - Group 3 and Group 4 – MET61 (according to protocol)

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

*Blood will be drawn prior to vaccinations.

Results

Table 82; Primary Immunogenicity Objective - Non-inferiority of hSBA vaccine seroresponse rate 30 days after the second dose of MenACYW conjugate vaccine or MENVEO (Group 1 vs Group 2) - Per-Protocol Analysis Set 2

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

n: number of subjects who achieve an hSBA vaccine seroresponse; M: number of subjects with available data for the relevant endpoint.
N: number of subjects in per-protocol analysis set for second year of life vaccination
95% CI of the single proportion calculated from the exact binomial method; 95% CI of the difference calculated from the Wilson Score method without continuity correction
hSBA vaccine seroresponse is defined as a post-vaccination titer >= 1:16 for subjects with pre-vaccination hSBA titer < 1:8,
or a post-vaccination titer >= 4-fold increase from baseline for subject with pre-vaccination hSBA titer >= 1:8
The overall non-inferiority will be demonstrated if the lower limit of the 2-sided 95% CI is > -10% for all four serogroups.
Group 1: MenACYW conjugate vaccine + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Group 2: MENVEO + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
Study: MET61 Program: t081761o179.sas Datasets=ADSL ADIS Output: PRODOPS/SP0047/MET61/CSR_01/REPORT/OUTPUT/T08176_i.rtf (08MAR2024 15:29)

Study objectives did not include the immunogenicity response to vaccinations concomitantly administered with meningococcal vaccines and no results on immunogenicity were reported for these concomitant vaccines.

Clinical studies in special populations

In Study MET58, subgroup analysis by gestational age was not performed as less than 30 subjects were born at preterm in the study (29 preterm subjects [1.7%] were included).

However, in Study MET42 (see section supportive studies for study design), analysis by preterm and full-term birth status was conducted:

Table 83: Summary of geometric means of hSBA titres by preterm and full-term - Per-Protocol Analysis Set 1

		Preterm						Full-term					
		Group 1 (N=66)			Group 2 (N=28)			Group 1 (N=861)			Group 2 (N=432)		
Serogroup	Time Point	M	GMT	95% CI	M	GMT	95% CI	M	GMT	95% CI	M	GMT	95% CI
A	D0 before 1st dose	51	3.31	(2.72 ; 4.02)	22	2.74	(2.23 ; 3.37)	671	3.37	(3.19 ; 3.55)	328	3.03	(2.84 ; 3.24)
	D30 after 3rd dose	55	17.7	(12.0 ; 26.1)	22	19.9	(9.32 ; 42.7)	796	26.0	(23.2 ; 29.2)	387	14.8	(12.8 ; 17.3)
C	D0 before 1st dose	55	2.54	(2.02 ; 3.20)	24	2.31	(1.99 ; 2.68)	703	2.77	(2.60 ; 2.94)	347	2.64	(2.46 ; 2.83)
	D30 after 3rd dose	57	411	(309 ; 548)	25	77.7	(43.2 ; 140)	777	389	(353 ; 428)	396	51.7	(44.6 ; 59.9)
Y	D0 before 1st dose	51	2.81	(2.30 ; 3.43)	25	2.87	(2.04 ; 4.04)	703	2.95	(2.75 ; 3.15)	348	2.87	(2.62 ; 3.15)
	D30 after 3rd dose	60	92.6	(70.2 ; 122)	24	58.7	(35.7 ; 96.6)	800	87.8	(80.5 ; 95.8)	399	39.7	(34.9 ; 45.2)
W	D0 before 1st dose	59	2.95	(2.35 ; 3.70)	25	2.43	(1.91 ; 3.09)	715	2.86	(2.69 ; 3.05)	360	2.66	(2.48 ; 2.85)
	D30 after 3rd dose	63	80.6	(59.4 ; 109)	27	70.9	(42.4 ; 119)	819	99.5	(92.2 ; 107)	411	47.6	(41.9 ; 54.0)

N: number of subjects in per-protocol analysis set 1, for infant vaccinations
M: number of subjects with valid serology results for the particular serogroup and time point
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines
Group 2: MENVEO® and routine pediatric vaccines
Preterm infant born at gestational age <37 weeks ; full-term infant born at gestational age >=37 weeks
For one subject, gestational age was not collected.

Table 84: Distribution of hSBA titres by preterm and full-term at D30 after the 6-month vaccinations - Per-Protocol Analysis Set 1

		Preterm				Full-term			
		Group 1 (N=66)		Group 2 (N=28)		Group 1 (N=861)		Group 2 (N=432)	
Serogroup	hSBA Titers	n/M	%	n/M	%	n/M	%	n/M	%
A	<1:4	8/55	14.5	4/22	18.2	96/796	12.1	65/387	16.8
	>=1:4	47/55	85.5	18/22	81.8	700/796	87.9	322/387	83.2
	>=1:8	42/55	76.4	16/22	72.7	621/796	78.0	261/387	67.4
	>=1:16	36/55	65.5	13/22	59.1	531/796	66.7	203/387	52.5
	>=1:32	23/55	41.8	11/22	50.0	424/796	53.3	153/387	39.5
	>=1:64	13/55	23.6	7/22	31.8	296/796	37.2	92/387	23.8
	>=1:128	7/55	12.7	4/22	18.2	198/796	24.9	55/387	14.2
	>=1:256	3/55	5.5	2/22	9.1	103/796	12.9	25/387	6.5
	>=1:512	2/55	3.6	2/22	9.1	57/796	7.2	7/387	1.8
	>=1:1024	0/55	0	0/22	0	15/796	1.9	1/387	0.3
	>=1:2048	0/55	0	0/22	0	1/796	0.1	0/387	0
C	<1:4	0/57	0	2/25	8.0	6/777	0.8	22/396	5.6
	>=1:4	57/57	100	23/25	92.0	771/777	99.2	374/396	94.4
	>=1:8	57/57	100	23/25	92.0	769/777	99.0	361/396	91.2
	>=1:16	57/57	100	23/25	92.0	759/777	97.7	335/396	84.6
	>=1:32	56/57	98.2	22/25	88.0	749/777	96.4	291/396	73.5
	>=1:64	53/57	93.0	19/25	76.0	723/777	93.1	223/396	56.3
	>=1:128	51/57	89.5	12/25	48.0	681/777	87.6	155/396	39.1
	>=1:256	49/57	86.0	8/25	32.0	601/777	77.3	75/396	18.9
	>=1:512	38/57	66.7	2/25	8.0	443/777	57.0	35/396	8.8
	>=1:1024	15/57	26.3	0/25	0	287/777	36.9	9/396	2.3
	>=1:2048	4/57	7.0	0/25	0	76/777	9.8	0/396	0
	>=1:4096	1/57	1.8	0/25	0	33/777	4.2	0/396	0
	>=1:8192	0/57	0	0/25	0	11/777	1.4	0/396	0
	>=1:16384	0/57	0	0/25	0	4/777	0.5	0/396	0
	>=1:32768	0/57	0	0/25	0	1/777	0.1	0/396	0
Y	<1:4	0/60	0	1/24	4.2	8/800	1.0	15/399	3.8
	>=1:4	60/60	100	23/24	95.8	792/800	99.0	384/399	96.2
	>=1:8	59/60	98.3	23/24	95.8	786/800	98.3	365/399	91.5
	>=1:16	59/60	98.3	23/24	95.8	755/800	94.4	334/399	83.7
	>=1:32	53/60	88.3	19/24	79.2	695/800	86.9	275/399	68.9
	>=1:64	51/60	85.0	15/24	62.5	565/800	70.6	187/399	46.9
	>=1:128	27/60	45.0	10/24	41.7	407/800	50.9	110/399	27.6
	>=1:256	15/60	25.0	4/24	16.7	233/800	29.1	47/399	11.8
	>=1:512	6/60	10.0	0/24	0	103/800	12.9	17/399	4.3
	>=1:1024	2/60	3.3	0/24	0	26/800	3.3	1/399	0.3
	>=1:2048	0/60	0	0/24	0	2/800	0.3	0/399	0
	>=1:4096	0/60	0	0/24	0	1/800	0.1	0/399	0
W	<1:4	1/63	1.6	0/27	0	3/819	0.4	13/411	3.2
	>=1:4	62/63	98.4	27/27	100	816/819	99.6	398/411	96.8
	>=1:8	61/63	96.8	27/27	100	809/819	98.8	380/411	92.5
	>=1:16	60/63	95.2	25/27	92.6	795/819	97.1	354/411	86.1
	>=1:32	57/63	90.5	21/27	77.8	747/819	91.2	312/411	75.9
	>=1:64	45/63	71.4	15/27	55.6	632/819	77.2	225/411	54.7
	>=1:128	26/63	41.3	14/27	51.9	460/819	56.2	130/411	31.6
	>=1:256	16/63	25.4	6/27	22.2	240/819	29.3	55/411	13.4
	>=1:512	7/63	11.1	4/27	14.8	95/819	11.6	19/411	4.6
	>=1:1024	2/63	3.2	0/27	0	22/819	2.7	5/411	1.2
	>=1:2048	0/63	0	0/27	0	0/819	0	1/411	0.2

n: number of subjects experiencing the endpoint listed in the first 3 columns
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 and routine pediatric vaccines
Group 2: MENVEO® and routine pediatric vaccines
Preterm infant born at gestational age <37 weeks ; full-term infant born at gestational age >=37 weeks
For one subject, gestational age was not collected.

Immune responses elicited by MenQuadfi given as three primary doses at 2, 4, and 6 months of age followed by a booster dose in the second year of life in infants with a history of preterm birth (31 to <37 weeks gestational age) (N=61-71) were compared to infants who were born full term in study MET42.

Table 85: Seroprotection rates (hSBA titre ≥1:8) in infants with a history of preterm vs full term birth (study MET42)

Serogroup	Study timepoint	Preterm (GA 31 to <37 weeks)	Full term (GA ≥37 weeks)

		Group 1a* (N=45)	Group 1b** (N=26)	Group 1a* (N=602)	Group 1b** (N=269)
A	D30 after primary series	65.7 (47.8; 80.9)	85.7 (63.7; 97.0)	78.1 (74.3; 81.6)	76.3 (70.3;81.5)
	D0 before booster dose	57.1 (41.0; 72.3)	62.5 (40.6; 81.2)	59.1 (55.0; 63.2)	55.6 (49.3; 61.7)
	D30 after booster dose	88.9 (73.9; 96.9)	84.2 (60.4; 96.6)	87.6 (84.7; 90.1)	93.2 (89.4; 95.9)
C	D30 after primary series	100 (90.5; 100)	100 (84.6; 100)	99.0 (97.7; 99.7)	98.7 (96.3; 99.7)
	D0 before booster dose	91.1 (78.8; 97.5)	73.1 (52.2; 88.4)	93.1 (90.7; 95.0)	84.7 (79.8; 88.8)
	D30 after booster dose	100 (91.0; 100)	100 (80.5; 100)	99.4 (98.3; 99.8)	99.3 (97.4; 99.9)
W	D30 after primary series	100 (91.0; 100)	91.7 (73.0; 99.0)	98.7 (97.3; 99.5)	98.4 (95.9; 99.6)
	D0 before booster dose	97.8 (88.2; 99.9)	88.5 (69.8; 97.6)	97.2 (95.5; 98.3)	95.9 (92.8; 97.9)
	D30 after booster dose	100 (90.5; 100)	100 (81.5; 100)	99.3 (98.3; 99.8)	100 (98.6; 100)
Y	D30 after primary series	100 (91.0; 100)	95.2 (76.2; 99.9)	98.5 (97.0; 99.3)	98.7 (96.4; 99.7)
	D0 before booster dose	97.6 (87.4; 99.9)	92.3 (74.9; 99.1)	96.8 (95.0; 98.1)	95.9 (92.8; 97.9)
	D30 after booster dose	100 (91.0; 100)	100 (81.5; 100)	99.0 (97.9; 99.6)	99.3 (97.4; 99.9)

* Group 1a: MenQuadfi and routine vaccines at 2,4,6, and 12-15 months of age.
** Group 1b: MenQuadfi at 2,4,6, and 15-18 months and routine vaccines at 2,4,6, 12-15 months of age, and 15-18 months of age.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

MenQuadfi is currently authorised for individuals from the age of 12 months and older. The purpose of the current procedure is to extend the indication to individuals from the age of 6 weeks.

This application comprises data from 6 completed studies. None of those investigated efficacy, and only 5 of those investigated immunogenicity (MET58, MET33, MET52, MET42, and MET61), which is acceptable as a widely accepted immunological correlate of protection for meningococcal vaccines containing serogroups A, C, W and Y exists (while an hSBA titre ≥ 1:8 is a common measure of seroprotection in the evaluation, an hSBA titre ≥ 1:4 is generally accepted as a clinical correlate of protection. Both thresholds have been used to infer vaccine-mediated immunologic protection against IMD, with the more conservative measure of ≥ 1:8). This approach has also been used for extending the indication to paediatric population from 6 weeks of age for the conjugated meningococcal vaccine Nimenrix (Procedure No. EMEA/H/C/002226/II/0049), and is in line with relevant EMA (EMEA/CHMP/VWP/164653/05 Rev. 1) and WHO guidance (Annex 9, Guidelines on clinical evaluation of vaccines: regulatory expectations).

Comparator(s)

Study MET58 is considered as pivotal evidence, the other studies are considered to be of supportive value. This is because among the submitted studies, only study MET58 investigated comparison of MenQuadfi to Nimenrix (Meningococcal group A, C, W-135, and Y conjugate vaccine), which is approved in the EU for individuals from the age of 6 weeks, whilst studies MET33, MET42, and MET61 applied MenACWY comparators (Menveo, Menactra) that are not approved in the EU for the relevant population (aged 6 weeks to 12 months). In the EU, Menveo is only authorised for administration to children starting from 2 years of age and it is critically noted that in the procedure initially intended to extend the Menveo indication to children aged 2 - 23 months (Procedure no. EMEA/H/C/001095/II/0018), a positive risk balance in that population could not be established; this was also stated in the scientific advice given in 2023 (Case No.: EMA/SA/0000114629). Menactra (Meningococcal (Serogroups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine) was administered with 2-dose regimen in Group 4 of study MET61 in toddlers but is not approved in the EU (and in the US only for children from 9 through 23 months of age, two doses, three months apart). Study MET52 had no MenACWY comparator but investigated concomitant vaccination with MenB vaccination (Bexsero).

Dose regimen

Different MenQuadfi dose regimens/vaccination schedules were investigated in the 5 immunogenicity studies:

- 3-dose (2+1 booster) regimen (studies **MET58** [at 2, 4, and 12 months of age] and MET33 [at 2, 6, and 12 months of age])
- 2-dose (1+1 booster) regimen (studies MET52, MET61)
- 4-dose (3+1 booster) regimen (Study MET42 and Group 4 of Study **MET58** [at 2, 4, 6, and 12 months of age]).

The MAH intends a 3-dose (2+1) regimen (two doses with an interval of at least 2 months in infancy which constitutes the primary immunisation, and an additional 3rd dose in the second year of life (from 12 months of age) at least 2 months after the last (second) dose for individuals starting meningococcal vaccination with 6 weeks of age and below 12 months of age.

In the scientific advice given in 2017 (Procedure No.: EMEA/H/SA/3131/1/FU/1/2017/II), the CHMP noted that one option would be the direct comparison of MenQuadfi using the 2+1 and 1+1 regimens to the approved Nimenrix with its 2+1 regimen, and, alternatively, the MAH could also include a 3+1 regimen of MenQuadfi as a more cautious approach.

Indeed, in study **MET58**, subjects in Group 1 and Group 3 were administered MenQuadfi using the 2+1 regimen, Group 3 was administered Nimenrix using the 2+1 regimen, and Group 4 was administered MenQuadfi using the 3+1 regimen. The first two administrations (i.e., in infancy below 12 months of age) of Groups 1, 2, 3, and 4 followed the posology of Nimenrix (i.e., for infants from 6 weeks to less than 6 months of age: two doses with an interval of 2 months between doses, plus a single booster dose at 12 months of age). In contrast to the posology of Nimenrix that clearly states that *"After completion of the primary immunisation course in infants 6 weeks to less than 12 months of age, a booster dose should be given at 12 months of age with an interval of at least 2 months after the last Nimenrix vaccination"*, the booster dose (i.e., 3rd administration for Groups 1, 2, and 3 and 4th administration for Group 4) was given from 12 to 18 months and thus with a considerable timely deviation from the Nimenrix posology. This aspect was of significant relevance for data analyses as the individual immune system may mount responses with different strength dependent on its maturation state. Upon request, the MAH explained the decision for the rather wide interval (compared to the

Nimenrix SmPC) and submitted additional data (e.g., Kaplan-Meier-curve) that indicate that the timing of the 3rd (booster) dose was comparable between treatment groups 1 and 2 and, additionally, that most participants received their 3rd dose between Month 12 and Month 14, which ameliorates potential concerns further. Hence, a potential uncertainty concerning potential differences in immunogenicity due to age between the groups, has not been substantiated.

Study population

1652 infants were planned to be randomised depending on the pneumococcal vaccine (10-valent pneumococcal polysaccharide conjugate vaccine PCV10 [Synflorix] or 13-valent pneumococcal polysaccharide conjugate vaccine PCV13 [Prevenar 13]) that was administered in the respective countries. 1432 subjects in countries where PCV10 was administered (i.e., Czech Republic, Romania, Sweden, Finland, and Poland) were planned to be randomised in a 1:1 ratio to either Group 1 (MenQuadfi) or Group 2 (Nimenrix). 220 subjects in countries where PCV13 was administered (i.e., Italy and Spain) were planned to be randomised in a 1:1 ratio to either Group 3 (MenQuadfi with 2+1 regimen) or Group 4 (MenQuadfi with 3+1 regimen). All other concomitant vaccines were the same. As a result of not randomising all groups (1-4) from the same pool, adequate comparisons can merely be made between Group 1 and 2 or Group 3 and 4 whereas comparisons between e.g. Group 1 and Group 3 or Group 4 are impaired considerably.

Overall, inclusion and exclusion criteria are acceptable to select the study population consisting of healthy male and female subjects aged 42 to 89 days at first visit, which were vaccination-naïve regarding any meningococcal vaccine (mono- or polyvalent, polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C, W, or Y; or meningococcal B serogroup-containing vaccine) and any pneumococcal, diphtheria, tetanus, pertussis, *Haemophilus influenzae* type B (Hib), poliovirus, measles, mumps, rubella, or hepatitis B vaccine. Influenza and rotavirus vaccines were allowed.

At least 1 major protocol deviation was reported for 332 subjects (46.5%) in Group 1, 333 subjects (45.9%) in Group 2, 38 subjects (33.9%) in Group 3, and 40 subjects (37.0%) in Group 4. The main reason for subjects not receiving MenQuadfi or Nimenrix was withdrawal by parent(s)/LAR(s). However, since the percentages of Group 1 and Group 2 differ only marginally, the percentages between Group 3 and Group 4 differ not to a significant extent and having in mind that the study population comprises infants or toddlers, this is expected and does not raise concerns.

Whilst percentage of males and females was similar in Group 1 and Group 2 (male/female ratio was 1.01 in Group 1 and 0.92 in Group 2), Group 3 and 4 differed in that regard (male/female ratio was 1.49 in Group 3 and 0.86 in Group 4). Moreover, mean age was similar between Group 1 and Group 2 (72.6 days (±12.2), 72.4 days (±12.1), respectively) and similar between Group 3 and Group 4 (62.5 days (±7.12), and 63.3 days (±7.93), respectively).

Objectives, endpoints & statistical considerations

For Study MET58, the primary analysis was comparison of hSBA geometric mean titres (GMTs) at Day 30 after the 3rd vaccination at 12 to 18-month between Group 1 and Group 2, and the most important secondary analysis comparison of the percentage of subjects with hSBA antibody titres >=1:8 at Day 30 after the 2nd vaccination at month 4-between Group 1 and Group 2. For both analyses, non-inferiority (NI) had to be achieved. The remaining objectives were analysed descriptively. The objectives and endpoints of the pivotal Study MET58 are overall acceptable for investigation of comparative immune responses between MenQuadfi and Nimenrix and effects on concomitant vaccination. It is noted that primary analysis and the most important secondary analysis were recommended in scientific advice (Procedure No.: EMEA/H/SA/3131/1/FU/1/2017/II), however, in different order. Moreover, since the MAH intends to list Rotavirus vaccination in 4.5 of the SmPC, it is

noted that investigation of effects on concomitant Rotavirus vaccination could have been an option for Study MET58, when considering that subjects in Finland, Sweden or Poland should have received the authorised rotavirus vaccine concomitantly with study vaccines at Visit 1 and Visit 2. In absence of MET58 data, only information gathered by studies MET33 and MET42, in which serum Rotavirus IgA was analysed, are available.

Meningococcal immune responses were analysed by primarily measuring hSBA antibody titres. Results were expressed using GMTs, seroprotection, or seroresponse. Seroprotection was defined as hSBA titres ≥1:8. The definition of seroresponse was for an individual with a pre vaccination titre < 1:8, the post-vaccination titre had to be ≥1:16, and for an individual with a pre vaccination titre ≥1:8, the post-vaccination titre had to be at least 4-fold greater than the pre vaccination titre. These thresholds/cut-offs are acceptable and were the same as for the initial MAA. Irrespective of the MAH's choice to analyse comparative GMTs as primary endpoint, all analyses, meaning also seroprotection and seroresponse are taken into consideration for the evaluation and to draw conclusions on the adequacy of the vaccine to protect against IMD caused by all 4 serogroups.

Sample size calculations were based on assumptions from a previous study (MET39) and appear plausible. Targeted power levels are in line with the need to meet all 4 co-primary endpoints simultaneously. Treatment allocation was performed using permuted block randomisation stratified by centre and age category. Group 1 and 2 were double-blind as regards the respective meningococcal vaccine administration. Group 3 and Group 4 were open-label as a result of the different administration schedules (MenQuadfi regimen 2+1 vs regimen 3+1 for Group 3 and Group 4, respectively). Concomitant vaccines were administered in an open-label manner as per local standard of care. This is all acceptable.

Planned statistical methods for study MET58 are acceptable and in line with standard practice for demonstrating NI immunogenicity of candidate vaccines when compared to an authorised active comparator. NI margins for GMTs (ratio >2/3) were pre-agreed, are consistent with margins applied in this setting and considered sufficient to permit inference of superior immunogenicity compared to a putative placebo (assay sensitivity) in case NI null hypotheses can be rejected. Statistical analyses were well defined for the primary and all secondary endpoints. Demonstration of non-inferior immune response based on comparing the two-sided 95% confidence interval to the pre-specified NI margin is acceptable. Main immunogenicity analyses were to be performed on the PPAS, specifically PPAS2 for the 2+1 scheme, which is acceptable for the purpose of demonstrating NI immune response. As regards multiplicity, primary endpoints concerning immune response with respect to the four investigated serotypes were considered co-primary implying that all four NI null hypotheses need to be rejected in order to make a claim on any one of them while controlling the multiple type I error. Multiplicity with respect to secondary hypotheses was controlled in a hierarchical manner, i.e., corresponding null hypotheses can only be rejected if all primary hypotheses are rejected first. Moreover, statistical analyses for objectives 2, 3, 4, 5, 6 and the observational immunogenicity objective were considered descriptive and therefore do not meet evidentiary standards to support confirmatory claims. This also applies to any post-hoc analyses included after conclusion of the study.

Initially, only a later version of the study protocol was submitted by the MAH; the full version history and a corresponding list of changes were subsequently provided upon request. Protocol version 6.0 introduced a sample size increase when about 75% of the originally planned participants had been recruited. On request, the MAH clarified this trial adaptation was based solely on a review of operational data, without consideration of immunogenicity or efficacy outcomes, which is not considered to impact study integrity.

Efficacy data and additional analyses

Meningococcal vaccination

In the pivotal study MET58, for the primary objective, hSBA GMT antibody response at Day 30 after the 3rd dose (2+1 regimen, at 12-15 months of age), was higher in Group 1 (MenQuadfi) than in Group 2 (Nimenrix): GMTs: 565 [95% CI: 505; 632] vs 120 [95% CI: 106; 135], 285 [95% CI: 260; 313] vs 160 [95% CI: 145; 177], 423 [95% CI: 382; 468] vs 275 [95% CI: 247; 305], for serogroup C, Y, and W, respectively. In contrast, for serogroup A, the hSBA GMT (Day 30 after the 3rd dose) was lower in the MenQuadfi group than that the Nimenrix group (131 [95% CI: 113; 151] vs 189 [95% CI: 165; 218], respectively). As mentioned above, since immune response with respect to the four investigated serotypes were considered co-primary implying that all four NI null hypotheses need to be rejected in order to make a claim on any one of them while controlling the multiple type I error, the primary objective to demonstrate non-inferiority of MenQuadfi and Nimenrix as regards hSBA GMT antibody response at Day 30 after the 3rd dose was not achieved.

As regards secondary objective #1 of study MET58 to demonstrate non-inferiority in terms of the percentage of subjects with hSBA antibody titres >=1:8 (i.e., the threshold considered to confer seroprotection) at Day 30 after the 2nd dose (i.e., 4-month vaccination) of MenQuadfi against the comparator Nimenrix, percentages were numerically higher in the MenQuadfi group (Group 1) than in the Nimenrix group (Group 2), i.e., 98.8% [95% CI: 97.5%; 99.6%] vs 91.9% [95% CI: 89.3%; 94.1%], 96.5% [95% CI: 94.5%; 97.9%] vs 93.5% [95% CI: 91.0%; 95.5%], 96.5% [95% CI: 94.6%; 97.9%] vs 94.5% [95% CI: 92.1%; 96.3%], for serogroup C, Y, and W, respectively. However, for serogroup A, the percentage was lower in the MenQuadfi group than in the Nimenrix group, i.e., 63.6% [95% CI: 59.2%; 67.8%] vs 75.8 [95% CI: 71.8%; 79.5%], respectively. Consequently, also the secondary objective #1 was not achieved and thus, together with the primary objective, both/all non-descriptive analyses.

Those findings are corroborated by additional descriptive data of MenQuadfi versus Nimenrix as regards hSBA antibody responses against the meningococcal A, C, W, and Y serogroups in a 3-dose series (secondary objective #4). Moreover, subgroup analyses regarding sex (female/male) and age group (42-59 days / 60-89 days) did not indicate striking differences between MenQuadfi and Nimenrix.

The MAH provided a post-hoc analysis of study MET58 data (non-inferiority of the hSBA vaccine seroresponse rate at D30 after the 12 to 18-month vaccination compared to D0 before the 2-month vaccination for Group 1 versus 2 - Per-Protocol Analysis Set 2). Indeed, percentages were similar for serogroups C, Y, and W between Group 1 (MenQuadfi) and Group 2 (Nimenrix) but also for Serogroup A, with 90.6% (95% CI: 87.8%; 92.9%) and 91.7% (95% CI: 89.1%; 93.8%), respectively. However, albeit this is per se a relevant information, it is noteworthy that since the 3rd dose serves as booster, such results are expected and thus comparison of seroresponse rates after the booster dose is of minor importance compared to GMTs (at Day 30 after the final dose) or other analyses after the 1st or 2nd dose.

Hence, in summary, although it can be concluded that MenQuadfi elicits immune responses of at least similar magnitude as the comparator Nimenrix for serogroups C, Y, and W, this is not the case for Serogroup A. The pivotal study failed to meet the pre-specified non-inferiority objectives (i.e., both the primary objective and secondary objective #1). Most concerning is the fact that the most sensitive endpoint after the 3rd (booster) dose, i.e. GMT, as well as the most relevant endpoint from a clinical perspective, i.e. seroprotection after the second dose (last infant dose), failed to show non-inferior immune response against serogroup A. Consequently, the MAH was asked to justify how the benefit/risk can be considered positive in the population of infants from 6 weeks to 12 months of age,

specifically taking into account that risk for severe disease is highest in the first year of life and that MenQuadfi is already approved from 12 months of age and older.

No new data were provided by the MAH's response; several arguments were noted by the MAH. Indeed, seroprotection curves for serogroups C, W, and Y indicated that MenQuadfi reaches close to 100% seroprotection earlier and maintains high levels, whereas comparator titres (Nimenrix) decreased between dose 2 and the booster (3rd dose). Albeit this was acknowledged, the data did not show a similar pattern for serogroup A. The MAH further noted that according to the most recent (2023) ECDC data the three serogroups of epidemiologic importance (after serogroup B, which is not included in MenQuadfi) in Europe were serogroups C, W and Y and that the results should be considered in a public health relevance context. Although this was acknowledged, since – based on ECDC data – invasive meningococcal disease (IMD) cases for serogroup A are either absent or extremely rare, nevertheless, a vaccine is expected to protect against any serogroup included, which is also reflected by the indication wording of MenQuadfi specifically mentioning A, C, W and Y.

Considering that the lower seroprotection rates elicited towards serogroup A as well as the lower GMTs, the need for an additional dose seemed obvious. Indeed, as regards serogroup A, the seroprotection rate after the last infant dose in Group 4 of study MET58 that investigated the MenQuadfi 3+1 regimen (i.e., Day 30 post dose 3 given at Month 6) was higher than the seroprotection rate of Group 1 (MenQuadfi 2+1) at Day 30 after the last (i.e., 2nd) infant dose (given at Month 4) and more comparable to the seroprotection rate elicited by Nimenrix (2+1 regimen, Group 2) at Day 30 after the last (i.e., 2nd) infant dose (given at Month 4), with 81.8% (95% CI: 72.2%; 89.2%) vs. 63.6% (95% CI: 59.2%; 67.8%) vs. 75.8% (95% CI: 71.8%; 79.5%), respectively. Upon request, the MAH proposed amendments of SmPC sections 4.2, 4.4 and 5.1, which were considered adequately reflecting that, because of lower antibody titres against serogroup A observed after the second dose at 4 months of age when compared with Nimenrix, an additional dose of MenQuadfi given at 6 months of age may be considered for infants who are expected to be at increased risk of invasive meningococcal disease due to exposure to serogroup A. These amendments were deemed appropriate to allow NITAGs to make recommendations for both the use of the vaccine and the vaccination regimen that is most applicable in certain epidemiological situations, lifestyle (e.g. travelling to areas with higher serogroup A incidence than in Europe) and certain risk groups.

Concomitant vaccination

A potential impact on concomitant vaccinations by meningococcal vaccination was analysed with the intention to amend the SmPC to include the information that MenQuadfi can be co-administered with "*measles-mumps-rubella vaccine (MMR) + varicella vaccine (V); combined diphtheria - tetanus - acellular pertussis (DTaP) vaccines, including combination DTaP vaccines containing hepatitis B vaccine (HepB), inactivated poliovirus (IPV) or Haemophilus influenzae type b (Hib) components such as DTaP-IPV-HepB-Hib or DTaP-IPV/Hib vaccine (in which the Hib component in each vaccine is conjugated to tetanus toxoid); 10-valent pneumococcal polysaccharide conjugated vaccine (PCV10); 13-valent PCV (PCV13); and rotavirus vaccine."* Descriptive data were presented intended to support these claims.

Tetanus, Diphtheria, Pertussis, Poliovirus, Haemophilus influenzae type b (Hib), Hepatitis B, Measles, Mumps, Rubella, pneumococcal 10-valent vaccine

In study MET58, this was investigated by Secondary Objective #2: antibody responses against meningococcal A, C, Y, and W serogroups after a 3-dose series of MenACYW Conjugate Vaccine (Group 3) and Secondary Objective #3: antibody responses against the antigens of the concomitant routine vaccines after a 3-dose series of MenACYW Conjugate Vaccine versus Nimenrix (Groups 1, 2, and 3). There was no actual investigation of the impact of the hexavalent vaccine(s) (Hexyon or Hexacima were applied, both virtually identical combined diphtheria, tetanus, acellular pertussis, inactivated

poliovirus, hepatitis B and *Haemophilus influenzae* type b vaccines, DTaP-IPV-HB-Hib), the MMR vaccine (Measles, Mumps, Rubella; M-M-RVAXPRO), or PCV10 (10-valent pneumococcal polysaccharide conjugated vaccine, Synflorix) on MenQuadfi vaccination or vice-versa, such as with a design comparing MenQuadfi + concomitant vaccines vs. concomitant vaccines solely vs. MenQuadfi alone (i.e., 3 treatment arms); however, no apparent differences as regards those concomitant vaccines' immune responses were reported between Group 1 (MenQuadfi) and Group 2 (Nimenrix) in study MET58. In previous scientific advice, it had been stated that it is important that immunogenicity of MenQuadfi and Nimenrix is primarily compared when given with the hexavalent combined DTaP-HBV-IPV-Hib vaccine Infanrix hexa and the 10-valent pneumococcal conjugate vaccine (PCV10) Synflorix, since these are known to have no important effect on Nimenrix, and that non-inferiority between MenQuadfi and Nimenrix would be needed to recommend co-administration of those. Of note, Infanrix hexa, Hexyon or Hexacima are all hexavalent and indicated for immunisation against the same pathogens but Infanrix hexa differs from Hexyon or Hexacima in antigen content, antigen quantity, adjuvant type, adjuvant content and production (different organisms),as well as the conjugated saccharide antigen of *Haemophilus influenzae* type b for which the current effective Guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1) specifically states that "*variable enhancement or depression of immune responses to conjugated saccharides has been observed when the carrier proteins for co-administered products are the same or different so that the specific type of conjugate for which data are available should be stated in the SmPC.*"

Although, technically, non-inferiority was not met (as noted above), in light of the comparable immune responses elicited by the hexavalent vaccines Hexyon or Hexacima and PCV10 (Synflorix) in Group 1 and 2, and immune responses elicited by MenQuadfi of at least similar magnitude as Nimenrix for serogroups C, Y and W, together with the additional (3rd) infant dose for those at risk of IMD caused by serogroup A, it appears justified that the information that MenQuadfi can be co-administered with hexavalent DTaP-IPV-HB-Hib vaccines Hexyon or Hexacima and PCV10 Synflorix is included in the SmPC. In contrast, this cannot be considered justified for the hexavalent combined DTaP-HBV-IPV-Hib vaccine Infanrix hexa as a result of the absence of data (Infanrix hexa was only administered in study MET52 but immune responses against its targeted pathogens were not analysed even though blood samples were taken to analyse anti-meningococcal titres) and the aforementioned differences as regards vaccine content.

As regards the MMR vaccine M-M-RVAXPRO, no data relevant for the population aged 6 weeks to below 12 months of age were presented because it was administered at Visit 4 at 12 months of age. Therefore, a pertinent statement in the SmPC was restricted to individuals 12 months of age or older.

Immunogenicity of vaccination with pentavalent vaccines (DTaP-IPV/Hib; Pentacel, Pentaxim) was investigated in Study MET33 (Russian cohort), Study MET42, and Study MET61. In Study MET33, for the Russian cohort, MenQuadfi doses were given at 3, 6, and 12 months of age and thus not according to the regimen currently intended by the MAH; additionally, no actual investigation of the impact of vaccination with Pentaxim on MenQuadfi vaccination or vice-versa (such as with a [3-arm] design comparing MenQuadfi + Pentaxim vaccine vs. Pentaxim alone vs. MenQuadfi alone) was applied. In Study MET42, Pentacel was administered concomitantly with MenQuadfi or Menveo at 2, 4, and 6 months of age (in infancy). However, there was also no actual investigation of the impact of vaccination with Pentacel on MenQuadfi vaccination or vice-versa (such as with a 3-arm design comparing MenQuadfi + Pentacel vaccine vs. Pentacel alone vs. MenQuadfi alone), and Menveo is not EU-approved for the population aged 6 weeks to below 12 months. In Study MET61, MenQuadfi doses were given at 6-7, and 12 months (1+1 regimen) and thus not according to the regimen currently intended by the MAH; additionally, no actual investigation of the impact of vaccination with Pentacel on MenQuadfi vaccination or vice-versa (such as with a the aforementioned 3-arm design) was applied, and again the comparator Menveo is not authorised in the EU for the population aged 6 weeks to below

12 months. Hence, concomitant vaccination with DTaP-IPV/Hib was also not considered substantiated. In addition, the arguments regarding different vaccine content noted above apply.

PCV10 vs PCV13

Group 1 and Group 3 of study MET58 both received MenQuadfi with the 2+1 regimen and differed regarding the use of the pneumococcal vaccine (Group 1: PCV10, 10-valent, Synflorix; Group 3: PCV13, 13-valent, Prevenar 13), all other concomitant vaccines were the same. There was no actual investigation of the impact of the PCV13 on MenQuadfi vaccination or vice-versa, such as with a 3-arm design comparing MenQuadfi + concomitant vaccines including PCV13 vs. concomitant vaccines including PCV13 vs. MenQuadfi alone. Furthermore, although Group 1 and Group 3 were included in the same study, subjects were from different countries and not randomised from the same pool (see study population above), which hampers a sound comparison and conclusion. Indeed, immune responses differed between Group 1 and Group 3 for some of the serotypes included in PCV13 compared to PCV10 (see serotypes 1, 5, 6B, 9V and 23F). However, seroresponse and protection rates seem comparable across groups 1 and 3 for MenQuadfi (indicating adequate response to included meningococcal serogroups regardless of PCV10 or PCV13). In addition, the sample size of Group 3 was significantly lower than that of Group 1 (n=716 vs n=110, at randomisation). At previous SA given, concerns regarding the co-administration with PCV13 were voiced, as co-administration of multiple polysaccharide-protein conjugates influences the immune response and therefore complicates the non-inferiority assessment vs. Nimenrix. In this regard, it is noted that the current effective Guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1) specifically states that "*variable enhancement or depression of immune responses to conjugated saccharides has been observed when the carrier proteins for co-administered products are the same or different*". Hence, the conclusion that it would not matter if PCV10 or PCV13 are administered concomitantly cannot be upheld.

Meningococcal Serogroup B (MenB)

The potential impact of vaccination with meningococcal serogroup B (Bexsero) was investigated in Study MET52, in which approximately 800 healthy infants aged ≥ 56 to ≤ 89 days were to be randomised 2:2:1 to receive either MenQuadfi at 3 months and at 12 to 13 months of age (1+1 regimen) and Bexsero at 2, 4, and 12 to 13 months of age (Group 1), MenQuadfi at 3 months and at 12 to 13 months of age and Bexsero at 2 and 4 months of age (Group 2, received 3rd dose Bexsero following completing of study procedures), or Bexsero at 2, 4, and 12 to 13 months of age (Group 3).

Of note, this study was already assessed in another type II variation (Procedure No. EMEA/H/C/005084/II/0027), which concluded that "*there was a very low number of patients providing samples at relevant baseline timepoints and visit 5 [last visit at 13-14 months of age], which are relevant for the estimation of the immune response (i.e. seroresponse). Additionally, the study does not address any potential influence of MenQuadfi on the immune response induced by Bexsero (MenB) or a possible effect of the initial Bexsero vaccination on serogroups included in MenQuadfi (i.e. A, C, Y and W), as no blood samples before Bexsero administration were analysed.*" It should be noted that 59.1% of evaluated participants had hSBA titres > 1:8 against serogroup A, 25.9% against serogroup C, 22.2% against serogroup Y, and 8.3% against serogroup W before first MenQuadfi administration at 3 months of age. It remains unclear whether this was due to cross reactivity of Bexsero vaccination at 2 months of age or external influence as no samples were taken to establish baseline levels before the first vaccination with Bexsero. In addition to that, the MenQuadfi regimen in Study MET52 is different (1+1) to the regimen that is intended by the MAH (2+1). The current statement in 4.5 of the SmPC "*There was no impact on the immune response to MenQuadfi when a meningococcal serogroup B vaccine was co-administered.*" was concluded based on data from Study MET59, in which MenB vaccines were administered concomitantly with the booster dose of MenQuadfi. Quite similarly, in Study MET52, MenQuadfi and Bexsero were concomitantly administered only at Visit 4 (at 12-13

months of age) at the time of the MenQuadfi booster dose in the 2+1 regimen. Actual data on concomitant vaccination of MenQuadfi and MenB below 12 months of age (and thus the age span relevant for this application/EoI) are not provided with this study (nor any other study in this application), albeit the Bexsero posology would have allowed concomitant vaccination with the 2+1 regimen of MenQuadfi (e.g., in Study MET58). As a consequence, the statement in the SmPC regarding MenB vaccination must be limited to those aged 12 months or older.

Varicella zoster virus (VZV/HHV-3)

Only subjects in Study MET42 received Varicella vaccination (Varivax). 96.0% of subjects in the MenQuadfi group reached the immune correlate of protection (at least 5 gpELISA units/mL). However, because Varicella vaccination was performed at Visit 5 at 12 months of age (as per Varivax SmPC), no data relevant for the population aged 6 weeks to below 12 months of age are presented. Therefore, the pertinent statement in the SmPC should be restricted to individuals 12 months of age or older. Besides, it is noted that MenQuadfi was administered using the 3+1 dose regimen (3rd dose at 6 months of age) and the comparator was Menveo instead of Nimenrix.

Rotavirus

Analyses of serum Rotavirus IgA was conducted in Study MET33 (only in subjects at sites in Mexico), and in Study MET42. MET33 study subjects received RotaTeq at 2, 4 and 6 months of age and MenQuadfi (Group 1) or Menveo (Group 2) at 2, 6 and 12 months of age (for comparison, in Study MET58 MenQuadfi was administered at 2, 4, and 12 months of age). In Study MET42, RotaTeq was administered to subjects at 2, 4, and 6 months of age, concomitantly with MenQuadfi or Menveo (which were administered at 2, 4, 6 and 12 months of age). Even though the study designs of the respective studies are not ideal to support robust conclusion, available results on MenACYW seroresponse and data on fold rise for rotavirus antibodies upon co-administration across studies are somewhat reassuring of an adequate immune response in studied infants. Also, no theoretical concerns seem evident that would indicate any specific risk. Thus, the co-administration of attenuated rotavirus vaccines can be supported and a respective information included in section 4.5 of the SmPC.

Immune responses in individuals with history of preterm birth

The MAH intended the following wording in 4.2 of the SmPC: "*Data indicate that MenQuadfi can be given with the same posology to infants with a history of preterm birth (< 37 weeks gestational age).*" Subgroup analysis by gestational age was not performed in Study MET58 as less than 30 subjects were born at preterm in the study (29 preterm subjects [1.7%]). In Study MET42, analysis by preterm and full-term birth status was conducted, however, this study applied a 4-dose (3+1; at 2, 4, 6, and 12 to 15 months of age) regimen, which was not intended by the MAH; moreover, the sample size of those preterm (in Study MET42) is rather low (preterm n=66 vs full term n=861). More importantly, no blood samples were taken after the 2nd dose and thus no immunogenicity analysis is available that would be required for comparison of immune responses (e.g., seroprotection rates) in infancy in accordance with the MAH's intended 2+1 dose regimen. To reflect the available information adequately, the paragraph in SmPC 4.2 was amended to "*Data from MenQuadfi given to infants with a history of preterm birth (31 to < 37 weeks of gestational age) with the same posology as infants born full term are limited. An additional primary dose of MenQuadfi may be considered appropriate for some individuals with history of preterm birth, see sections 4.8 and 5.1.*" and relevant data are presented in SmPC section 5.1.

2.4.3. Conclusions on the clinical efficacy

The primary aim of the pivotal study MET58 to demonstrate non-inferiority as regards immune responses against all serogroups included in MenQuadfi (serogroups A, C, W, and Y) with the initially proposed 2+1 vaccination regimen (2 doses in infancy + 1 booster dose) was not met, since overall results demonstrate lower relevant immune responses of serogroup A compared to the comparator Nimenrix.

Consequently, a recommendation to consider an additional (3rd) dose in the primary series in infancy at 6 months of age (in addition to two doses given at 2 months of age and 4 months of age) for infants who are expected to be at increased risk of invasive meningococcal disease due to exposure to serogroup A was introduced in SmPC sections 4.2 and 4.4, supported with informative data in section 5.1.

Multiple concomitant vaccinations have been investigated. However, co-administration as regards the population aged 6 weeks to below 12 months of age could only be substantiated for the hexavalent vaccines Hexyon or Hexacima (Tetanus, Diphtheria, Pertussis, Poliovirus, Hepatitis B, *Haemophilus influenzae* type b [Hib]), rotavirus vaccine (live attenuated), and Synflorix (PCV10).

From a clinical efficacy perspective this extension of indication is approvable.

2.5. Clinical safety

Introduction

Summary of the safety profile in the currently approved paediatric indication

The safety of a single dose of MenQuadfi in individuals 12 months of age and older was evaluated in clinical trials where 6 308 subjects received either a primary dose (N = 5 906) or a booster dose (N = 402) of MenQuadfi. This included 1 389 toddlers aged 12 through 23 months of age, 498 children aged 2 through 9 years, 2 289 children and adolescents aged 10 through 17 years.

The most frequently reported adverse reactions within 7 days after vaccination with a single dose of MenQuadfi alone in toddlers 12 through 23 months of age were irritability (36.7%) and injection site tenderness (30.6%) and in ages 2 years and above were injection site pain (38.7%) and myalgia (30.5%).

In toddlers 12 through 23 months of age, injection site erythema and swelling (very common) at the MenQuadfi injection site, vomiting (common) and diarrhoea (common), were reported more frequently than in the older age groups.

Methods

Data pooling

Six clinical studies that used the MenACYW conjugate vaccine containing 10 µg meningococcal capsular polysaccharides per serogroup as the final formulation already approved in the initial licensure were included in this Integrated Summary of Safety (ISS) analysis, targeting population of 6 weeks old and above in Mexico, the Russian Federation, the USA, Puerto Rico, the UK, Czech Republic, Romania, Sweden, Finland, Poland, Italy and Spain.

These six studies are MET33, MET41, MET42, MET52, MET58 and MET61.

For study MET61, participants in Group 3 and Group 4 (vaccination at 17-19 months and 20-23 months) will not be included in the ISS as this age group at the time of administration of the first dose is not relevant for this ISS.

Table 86: Summary table for safety data collection

	MET33*	MET41	MET42	MET52	MET58	MET61
Dose, schedule of vaccination	**Group1 and 3:** **2+1 doses (2-3, 6,12mos)** **Group 2:** **3+1 doses (2,4,6,12mos**	**3+1 doses (2,4,6,12mos)**	**3+1 doses (2,4,6,12-18mos)**	**1+1 doses (3,12-13mos)**	**Group1-3:** **2+1 doses (2,4,12-18mos)** **Group 4:** **3+1 doses (2,4,6,12-18mos)**	**Group 1 and Group 2: 1+1 doses (6,12-13mos)**
Age at 1st dose	**2mos**	**6 weeks**	**6 weeks**	**3 mos**	**6 weeks**	**6 mos**
Immediate AEs (minutes post vaccination)	30	30	30	30	30	30
Immediate ARs (minutes post vaccination)	30	30	30	30	30	30
Solicited injection site ARs (days post vaccination)	7	7	7	7	7	7
Solicited systemic ARs (days post vaccination)	7	7	7	7	7	7
Unsolicited AEs/ARs (days post vaccination)	30	30	30	30	30	30
Safety follow-up after last vaccination (days post vaccination)	30	180	180	30	30	180
SAEs	throughout the trial	throughout the trial	throughout the trial	throughout the trial	throughout the trial	throughout the trial
AESIs	throughout the trial	throughout the trial	throughout the trial	throughout the trial	throughout the trial	throughout the trial

* Group 4 of MET33 is not considered in this ISS as no MenACYW conjugate vaccine is administered in this Group.

Analysis populations

Six safety analysis sets (SafAS) were used to describe the safety results for MenACYW conjugate vaccine, Menveo and Nimenrix when administered either in a 2-dose (1+1), 3-dose (2+1) or 4-dose (3+1) schedule concomitantly with routine paediatric vaccines.

Table 87: Summary table of the analysis set used for each pooling

Pool	Analysis Set	Description
Pool 1	Safety Analysis Set post any dose (SafAS 1)	For safety analysis after any dose, regardless of dose received and age stage
Pool 2	Safety Analysis Set post any dose of infant vaccination (SafAS 2)	For safety analysis after any dose during the infant stage, regardless of dose received
Pool 3	Safety Analysis Set post dose 1 of infant vaccination (SafAS 3)	For safety analysis after the first dose during infant stage
Pool 4	Safety Analysis Set post dose 2 of infant vaccination (SafAS 4)	For safety analysis after the second dose during infant stage
Pool 5	Safety Analysis Set post dose 3 of infant vaccination (SafAS 5)	For safety analysis after the third dose during infant stage
Pool 6	Safety Analysis Set post booster dose (SafAS 6)	For safety analysis after the toddler dose during booster phase

General statistical approach

No hypotheses for safety were tested. Descriptive statistics were presented. The main parameters for the safety endpoints were described by 95% confidence interval (CI) using the exact binomial method (Clopper-Person method). For descriptive purposes, the following statistics were presented:

Exact 95% CIs for the single proportion and density incidence were calculated using the exact binomial method (Clopper- Pearson method, quoted by Newcombe, i.e., using the inverse of the beta integral with SAS). The 95% CIs of point estimates were calculated using normal approximation for quantitative data.

Safety assessment methods

Clinical safety was assessed in terms of immediate reactions, solicited injection site and systemic reactions, unsolicited non-serious adverse events (AEs)/adverse reactions (ARs), and serious adverse events (SAEs) including adverse events of special interest (AESIs).

The overall safety endpoints and their time windows for collection are presented in Table 1.

Table 88: Safety endpoints and time window for collection

Safety Endpoint	Data Collected and Collection Window
Immediate Unsolicited Adverse Events* (AEs)/Adverse Reactions (ARs)	0-30 minutes after vaccination by System Organ Class (SOC) and preferred term (PT)
Solicited (pre-defined) Injection Site Reactions	Within 7 days after vaccination (Day 0 to Day 07) by time of onset, number of days of occurrence, and maximum intensity
Solicited (pre-defined) Systemic Reactions	Within 7 days after vaccination (Day 0 to Day 07) by time of onset, number of days of occurrence, and maximum intensity
Unsolicited Non-Serious AEs/ARs	Within 30 days after vaccination (Day 0 to Day 30) by SOC and PT, time of onset, duration, and maximum intensity
Adverse Events of Special Interest (AESI): All and Related±	All AESIs were collected throughout the study as SAEs to ensure that the events were communicated to the Sponsor in an expedited manner and followed up until the end of the study period or resolution, as per the assigned causality
Serious Adverse Events (SAE)s: All And Related	SAEs were collected throughout the study to ensure that the events were communicated to the Sponsor in an expedited manner and followed up throughout the study period period or resolution, as per the assigned causality
Deaths	Occurring throughout the study period
AEs Leading To Discontinuation (Serious and Non-Serious)	AEs leading to discontinuation were collected within 30 days after vaccination (for non-serious AEs) and throughout the study period (for SAEs) By SOC and PT within 30 days after vaccination (for non-serious AEs) and throughout the study period (for SAEs)

* An AE is considered an adverse reaction (AR) when a causal relationship between the vaccine and an AE is at least a reasonable possibility
± In studies MET41, MET42, and MET61, SAEs (including AESIs) were followed up for 6 months after the last vaccinaton. In studies MET33, MET52, and MET58, SAEs (including AESIs) were followed up for 30 days after the last vaccinaton.

By definition, solicited reactions were to be considered as being related to the product administered. For injectable vaccines, solicited reactions can either be solicited injection site reactions or solicited systemic reactions.

Solicited injection site reactions and solicited systemic reactions in infants were recorded by the participant's parent(s) or other legally acceptable representative in the diary card on the day of vaccination and for the next 7 days (i.e., Day 0 to Day 7) until resolution.

Patient exposure

The total number of participants who received MenACYW conjugate vaccine, Menveo, and Nimenrix concomitantly with routine paediatric vaccines in studies MET33, MET41, MET42, MET52, MET58, and Groups 1 and 2 of MET61 is presented in Table 3.

Table 89: Overall extent of exposure

Study	Safety Analysis Sets	MenACYW + routine pediatric vaccines N	Menveo + routine pediatric vaccines N	Nimenrix + routine pediatric vaccines* N
Pooled MET33, MET41, MET42, MET52, MET58 and MET61	Safety analysis set post any dose (SafAS 1)	6060	2024	706
Pooled MET33, MET41, MET42, MET52, MET58 and MET61	Safety analysis set post any dose for infant vaccination (SafAS 2)	6060	2024	706
Pooled MET33, MET41, MET42, MET52, MET58 and MET61	Safety analysis set post dose 1 for infant vaccination (SafAS 3)	6060	2024	706
Pooled MET33, MET41, MET42 and MET58	Safety analysis set post dose 2 for infant vaccination (SafAS 4)	4880	1585	704
Pooled Group 2 of MET33, MET41, MET42 and Group 4 of MET58	Safety analysis set post dose 3 for infant vaccination (SafAS 5)	3598	1536	-
Pooled MET33, MET41, MET42, MET52, MET58 and MET61	Safety analysis set post booster dose (SafAS 6)	5373	1724	696

N: number of participants in the corresponding Safety Analysis Set
Contributing studies: MET33, MET41, MET42, MET52, MET58 and Group 1 and Group 2 of MET61
*Only Group 2 of MET58 was administrated with Nimenrix
Source: Modified from 5.3.5.3 Integrated Safety Summary Report Table 1

Demographics at baseline

Table 90: Summary of participant demographics at baseline – SafAS2

	MenACYW + routine paediatric vaccines (N=6060)	Menveo + routine paediatric vaccines (N=2024)	Nimenrix + routine paediatric vaccines (N=706)
Sex: n (%)			
Male	3162 (52.2)	1059 (52.3)	339 (48.0)
Female	2898 (47.8)	965 (47.7)	367 (52.0)
Missing	0	0	0
Sex ratio: Male/Female	1.09	1.10	0.92
Age (months)			
M	6060	2024	706
Mean (SD)	1.99 (1.11)	2.51 (1.69)	1.82 (0.387)
Min ; Max	1.00 ; 7.00	1.00 ; 7.00	1.00 ; 2.00
Median	2.00	2.00	2.00
Q1 ; Q3	1.00 ; 2.00	2.00 ; 2.00	2.00 ; 2.00
Racial origin: n (%)			
American Indian or Alaska Native	187 (3.1)	81 (4.0)	0
Asian	60 (1.0)	28 (1.4)	1 (0.1)
Black or African American	483 (8.0)	227 (11.2)	0
Native Hawaiian or Other Pacific Islander	16 (0.3)	11 (0.5)	1 (0.1)
White	5007 (82.6)	1550 (76.6)	682 (96.6)
Mixed origin	176 (2.9)	80 (4.0)	5 (0.7)
Not reported	84 (1.4)	35 (1.7)	15 (2.1)
Unknown	47 (0.8)	12 (0.6)	2 (0.3)
Ethnicity: n (%)			
Hispanic or Latino	1934 (31.9)	864 (42.7)	12 (1.7)
Not Hispanic or Latino	4040 (66.7)	1152 (56.9)	645 (91.4)
Unknown	74 (1.2)	5 (0.2)	47 (6.7)
Not Reported	12 (0.2)	3 (0.1)	2 (0.3)
Gestational age at birth: n (%) *			
Preterm birth	237 (5.0)	78 (5.0)	14 (2.0)
Full-term birth	4483 (94.9)	1484 (94.9)	692 (98.0)
Missing	3 (<0.1)	2 (0.1)	0

n: number of participants fulfilling the item listed in the first column
M: number of participants with available data for the relevant endpoint
N: number of participants in safety analysis set post any dose for infant vaccination
Percentages are based on N, except for percentages for gestation age at birth, which are based on number of participants in safety analysis set post any dose in study MET41, MET42 and MET58.
Q1; Q3: first quartile; third quartile. SD: standard deviation
Preterm infant born at gestational age <37 weeks (32 – 36 weeks of gestational age); full-term infant born at gestational age >=37 weeks
Contributing studies: MET33, MET41, MET42, MET52, MET58 and Group 1 and Group 2 of MET61
*Only MET41, MET42 and MET58 are considered
SafAS2 was defined as those participants who received at least 1 dose of the study vaccines from 2 to 7 months of age and had any safety data available.
Source: Modified from 5.3.5.3 Integrated Safety Summary Report Table 4.1.1.1

The mean age (± standard deviation [SD]) was 1.99 (±1.11) months in participants who received MenACYW conjugate vaccine, 2.51 (±1.69) months in participants who received Menveo, and 1.82 (±0.387) months in participants who received Nimenrix.

A total of 623 participants received a first dose of MenACYW conjugate vaccine, 188 participants a first dose of Menveo, and 113 participants a first dose of Nimenrix between 6 weeks and 8 weeks of age (before the age of 2 months, i.e. between 42 – 59 days). Of the participants who were vaccinated at 6 weeks (42 – 48 days) of age, 144 participants received MenACYW conjugate vaccine as their first vaccination, 39 participants received Menveo, and 51 participants received Nimenrix.

Table 91: Age distribution of participants at 42-59 days

Age (days)	MenACYW + routine paediatric vaccines (N=623)	Menveo + routine paediatric vaccines (N=188)	Nimenrix + routine paediatric vaccines (N=113)
42	14	5	2
43	23	6	8
44	25	5	7
45	21	3	7
46	24	7	11
47	13	6	7
48	24	7	9
49	19	5	4
50	16	3	3
51	17	4	2
52	23	7	4
53	27	6	6
54	23	11	11
55	33	7	5
56	57	19	8
57	49	20	7
58	66	21	7
59	149	46	5

N = number of participants in safety analysis set post any dose at 42 days - 59 days of age.

Source: Reproduced from 5.3.5.3 Post-hoc analysis for module 2.7.4 Table 1

The majority of participants from studies MET41, MET42, and MET58 were full-term at birth (94.9% participants who received MenACYW conjugate vaccine, 94.9% participants who received Menveo, and 98.0% participants who received Nimenrix). All participants from studies MET33, MET52 and MET61 were full-term at birth. A total of 237 MenACYW conjugate vaccine recipients (5.0%) from studies MET41, MET42, and MET58 were pre-term (31 – 36 weeks of gestational age) at birth.

Adverse events

Overview of adverse events after any dose

In each group, meningococcal vaccines were administered concomitantly with routine paediatric vaccines, therefore the safety profile represents this concomitant use.

Table 92: Safety overview after any vaccine injections - SafAS1

	MenACYW + routine paediatric vaccines (N=6060)			Menveo + routine paediatric vaccines (N=2024)			Nimenrix + routine paediatric vaccines (N=706)		
Participants experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Within 30 mins after any vaccine injections									

Participants experiencing at least one:	MenACYW + routine paediatric vaccines (N=6060) n/M	%	(95% CI)	Menveo + routine paediatric vaccines (N=2024) n/M	%	(95% CI)	Nimenrix + routine paediatric vaccines (N=706) n/M	%	(95% CI)
Immediate unsolicited AE	11/6060	0.2	(0.1 ; 0.3)	3/2024	0.1	(0 ; 0.4)	0/706	0	(0 ; 0.5)
Immediate unsolicited AR	5/6060	<0.1	(0 ; 0.2)	1/2024	<0.1	(0 ; 0.3)	0/706	0	(0 ; 0.5)
Solicited reaction from D0 to D7 within solicited period after any vaccine injections									
Solicited injection site reaction	4756/5898	80.6	(79.6 ; 81.6)	1502/1948	77.1	(75.2 ; 79.0)	632/705	89.6	(87.2 ; 91.8)
Solicited injection site reaction after injection of MenACYW or Menveo or Nimenrix	4276/5897	72.5	(71.4 ; 73.6)	1358/1948	69.7	(67.6 ; 71.7)	476/705	67.5	(63.9 ; 71.0)
Solicited injection site reaction after injection of Infanrix hexa	425/614	69.2	(65.4 ; 72.9)	-	-	-	-	-	-
Solicited injection site reaction after injection of Pentacel	2703/3864	70.0	(68.5 ; 71.4)	1136/1707	66.5	(64.3 ; 68.8)	-	-	-
Solicited injection site reaction after injection of Hexyon or Hexacima	867/1114	77.8	(75.3 ; 80.2)	59/99	59.6	(49.3 ; 69.3)	577/705	81.8	(78.8 ; 84.6)
Solicited injection site reaction after injection of Prevnar 13	3113/4426	70.3	(69.0 ; 71.7)	1323/1943	68.1	(66.0 ; 70.2)	-	-	-
Solicited injection site reaction after injection of Pentaxim	17/149	11.4	(6.8 ; 17.6)	-	-	-	-	-	-
Solicited injection site reaction after injection of Bexsero	264/296	89.2	(85.1 ; 92.5)	-	-	-	-	-	-
Solicited injection site reaction after injection of MMR *	1803/4096	44.0	(42.5 ; 45.6)	697/1589	43.9	(41.4 ; 46.3)	303/651	46.5	(42.7 ; 50.5)
Solicited injection site reaction after injection of Synflorix	596/696	85.6	(82.8 ; 88.2)	-	-	-	592/705	84.0	(81.1 ; 86.6)
Solicited injection site reaction after injection of Varivax	1246/2905	42.9	(41.1 ; 44.7)	653/1497	43.6	(41.1 ; 46.2)	-	-	-
Solicited injection site reaction after injection of ENGERIX-B or Recombivax HB	2311/3980	58.1	(56.5 ; 59.6)	972/1682	57.8	(55.4 ; 60.2)	-	-	-
Solicited injection site reaction after injection of Havrix	173/401	43.1	(38.2 ; 48.2)	-	-	-	-	-	-
Solicited injection site reaction after injection of Pediarix + ActHib or Hiberix or PedvaxHIB	77/139	55.4	(46.7 ; 63.8)	74/136	54.4	(45.7 ; 63.0)	-	-	-
Solicited systemic reaction	4910/5896	83.3	(82.3 ; 84.2)	1553/1948	79.7	(77.9 ; 81.5)	659/705	93.5	(91.4 ; 95.2)
Within 30 days after any vaccine injections									
Unsolicited AE	3603/6060	59.5	(58.2 ; 60.7)	1094/2024	54.1	(51.9 ; 56.2)	480/706	68.0	(64.4 ; 71.4)
Unsolicited AR	564/6060	9.3	(8.6 ; 10.1)	140/2024	6.9	(5.8 ; 8.1)	128/706	18.1	(15.4 ; 21.2)
Unsolicited non-serious AE	3576/6060	59.0	(57.8 ; 60.3)	1092/2024	54.0	(51.8 ; 56.1)	477/706	67.6	(64.0 ; 71.0)
Unsolicited non-serious AR	562/6060	9.3	(8.6 ; 10.0)	140/2024	6.9	(5.8 ; 8.1)	128/706	18.1	(15.4 ; 21.2)
Unsolicited non-serious injection site AR after injection of MenACYW or Menveo or Nimenrix	469/6060	7.7	(7.1 ; 8.4)	122/2024	6.0	(5.0 ; 7.2)	74/706	10.5	(8.3 ; 13.0)
Unsolicited non-serious injection site AR after injection of Infanrix hexa	51/617	8.3	(6.2 ; 10.7)	-	-	-	-	-	-
Unsolicited non-serious injection site AR after injection of Pentacel	262/4177	6.3	(5.6 ; 7.1)	77/1925	4.0	(3.2 ; 5.0)	-	-	-
Unsolicited non-serious injection site AR after injection of Hexyon or Hexacima	172/1117	15.4	(13.3 ; 17.7)	7/99	7.1	(2.9 ; 14.0)	142/706	20.1	(17.2 ; 23.3)

Participants experiencing at least one:	MenACYW + routine paediatric vaccines (N=6060) n/M	%	(95% CI)	Menveo + routine paediatric vaccines (N=2024) n/M	%	(95% CI)	Nimenrix + routine paediatric vaccines (N=706) n/M	%	(95% CI)
Unsolicited non-serious injection site AR after injection of Prevnar 13	296/4598	6.4	(5.7 ; 7.2)	101/2024	5.0	(4.1 ; 6.0)	-	-	-
Unsolicited non-serious injection site AR after injection of Pentaxim	0/149	0	(0 ; 2.4)	-	-	-	-	-	-
Unsolicited non-serious injection site AR after injection of Bexsero	46/308	14.9	(11.1 ; 19.4)	-	-	-	-	-	-
Unsolicited non-serious injection site AR after injection of MMR *	124/4872	2.5	(2.1 ; 3.0)	31/2024	1.5	(1.0 ; 2.2)	32/706	4.5	(3.1 ; 6.3)
Unsolicited non-serious injection site AR after injection of Synflorix	156/696	22.4	(19.4 ; 25.7)	-	-	-	152/706	21.5	(18.6 ; 24.7)
Unsolicited non-serious injection site AR after injection of Varivax	89/3606	2.5	(2.0 ; 3.0)	34/1925	1.8	(1.2 ; 2.5)	-	-	-
Unsolicited non-serious injection site AR after injection of ENGERIX-B or Recombivax HB	125/4326	2.9	(2.4 ; 3.4)	45/1925	2.3	(1.7 ; 3.1)	-	-	-
Unsolicited non-serious injection site AR after injection of Havrix	6/571	1.1	(0.4 ; 2.3)	-	-	-	-	-	-
Unsolicited non-serious injection site AR after injection of Pediarix + ActHib or Hiberix or PedvaxHIB	8/370	2.2	(0.9 ; 4.2)	4/361	1.1	(0.3 ; 2.8)	-	-	-
Unsolicited non-serious systemic AE	3339/6060	55.1	(53.8 ; 56.4)	1029/2024	50.8	(48.6 ; 53.0)	428/706	60.6	(56.9 ; 64.2)
Unsolicited non-serious systemic AR	120/6060	2.0	(1.6 ; 2.4)	19/2024	0.9	(0.6 ; 1.5)	63/706	8.9	(6.9 ; 11.3)
AE leading to study discontinuation	8/6060	0.1	(0.1 ; 0.3)	3/2024	0.1	(0 ; 0.4)	0/706	0	(0 ; 0.5)
SAE	120/6060	2.0	(1.6 ; 2.4)	21/2024	1.0	(0.6 ; 1.6)	16/706	2.3	(1.3 ; 3.7)
Death	4/6060	<0.1	(0 ; 0.2)	0/2024	0	(0 ; 0.2)	0/706	0	(0 ; 0.5)
AESI	10/6060	0.2	(0.1 ; 0.3)	0/2024	0	(0 ; 0.2)	0/706	0	(0 ; 0.5)
During 6-month follow-up period †									
SAE	55/4177	1.3	(1.0 ; 1.7)	19/1925	1.0	(0.6 ; 1.5)	-	-	-
Death	0/4177	0	(0 ; 0.1)	0/1925	0	(0 ; 0.2)	-	-	-
AESI	12/4177	0.3	(0.1 ; 0.5)	4/1925	0.2	(0.1 ; 0.5)	-	-	-
During the study									
SAE	291/6060	4.8	(4.3 ; 5.4)	72/2024	3.6	(2.8 ; 4.5)	57/706	8.1	(6.2 ; 10.3)
Death	4/6060	<0.1	(0 ; 0.2)	0/2024	0	(0 ; 0.2)	0/706	0	(0 ; 0.5)
AESI	36/6060	0.6	(0.4 ; 0.8)	9/2024	0.4	(0.2 ; 0.8)	3/706	0.4	(0.1 ; 1.2)

n: number of participants experiencing the endpoint listed in the first column; M: number of participants with available data for the relevant endpoint; Percentages are based on M.
N: number of participants in safety analysis set post any dose; "Immediate unsolicited AE" is collected only for immediate unsolicited systemic AEs.
"Unsolicited AE" also includes immediate and serious unsolicited AEs; "Unsolicited non-serious AE" includes any unsolicited AE that is non-serious.
AR: Reactions related to study vaccine (MenACYW/Menveo/Nimenrix); Unsolicited systemic reactions related to MenACYW/Bexsero after booster vaccination for group 1 of MET52 are considered as
related to MenACYW. Unsolicited injection site reactions related to NIMP (routine vaccines) are reported separately
Contributing studies: MET33, MET41, MET42, MET52, MET58 and Group 1 and Group 2 of MET61
*MMR refers to M-M-RII, M-M-RVAXPRO and locally licensed MMR or MM+R vaccines that are allowed to be administered in the included studies
†Only MET41, MET42 and Group 1 and Group 2 of MET61 are considered

Participants experiencing at least one:	MenACYW + routine paediatric vaccines (N=6060) n/M	%	(95% CI)	Menveo + routine paediatric vaccines (N=2024) n/M	%	(95% CI)	Nimenrix + routine paediatric vaccines (N=706) n/M	%	(95% CI)

SafAS1 was defined as those participants who received at least 1 dose of the study vaccines and had any safety data available
Source: Modified from 5.3.5.3 Integrated Safety Summary Report Table 3.2.1

Study MET58

Table 93: Safety overview after vaccine injections - Overall Safety Analysis Set for Any Dose

Subjects experiencing at least one:	Group 1 (N=696) n/M	%	(95% CI)	Group 2 (N=706) n/M	%	(95% CI)	Group 3 (N=112) n/M	%	(95% CI)	Group 4 (N=108) n/M	%	(95% CI)
Within 30 mins after any vaccine injections												
Immediate unsolicited AE	1/696	0.1	(0 ; 0.8)	0/706	0	(0 ; 0.5)	0/112	0	(0 ; 3.2)	1/108	0.9	(0 ; 5.1)
Immediate unsolicited AR	0/696	0	(0 ; 0.5)	0/706	0	(0 ; 0.5)	0/112	0	(0 ; 3.2)	1/108	0.9	(0 ; 5.1)
D0 to D7 after any vaccine injections	677/696	97.3	(95.8 ; 98.3)	680/705	96.5	(94.8 ; 97.7)	104/112	92.9	(86.4 ; 96.9)	103/106	97.2	(92.0 ; 99.4)
Solicited injection site reaction	628/696	90.2	(87.8 ; 92.3)	632/705	89.6	(87.2 ; 91.8)	95/112	84.8	(76.8 ; 90.9)	86/106	81.1	(72.4 ; 88.1)
Solicited injection site after injection of MenACYW or Nimenrix	494/696	71.0	(67.4 ; 74.3)	476/705	67.5	(63.9 ; 71.0)	72/112	64.3	(54.7 ; 73.1)	74/106	69.8	(60.1 ; 78.3)
Solicited injection site after injection of DTaP-IPV-HB-Hib	584/696	83.9	(81.0 ; 86.6)	577/705	81.8	(78.8 ; 84.6)	81/112	72.3	(63.1 ; 80.4)	71/106	67.0	(57.2 ; 75.8)
Solicited injection site after injection of Prevenar 13 or Synflorix	596/696	85.6	(82.8 ; 88.2)	592/705	84.0	(81.1 ; 86.6)	86/112	76.8	(67.9 ; 84.2)	72/106	67.9	(58.2 ; 76.7)
Solicited injection site after injection of M-M-RVAXPRO	291/643	45.3	(41.4 ; 49.2)	303/651	46.5	(42.7 ; 50.5)	39/105	37.1	(27.9 ; 47.1)	38/103	36.9	(27.6 ; 47.0)
Solicited systemic reaction	661/696	95.0	(93.1 ; 96.5)	659/705	93.5	(91.4 ; 95.2)	100/112	89.3	(82.0 ; 94.3)	96/106	90.6	(83.3 ; 95.4)
D0 to D30 after any vaccine injections												
Unsolicited AE	458/696	65.8	(62.1 ; 69.3)	480/706	68.0	(64.4 ; 71.4)	80/112	71.4	(62.1 ; 79.6)	79/108	73.1	(63.8 ; 81.2)
Unsolicited AR	128/696	18.4	(15.6 ; 21.5)	128/706	18.1	(15.4 ; 21.2)	10/112	8.9	(4.4 ; 15.8)	17/108	15.7	(9.4 ; 24.0)
Unsolicited non-serious AE	453/696	65.1	(61.4 ; 68.6)	477/706	67.6	(64.0 ; 71.0)	79/112	70.5	(61.2 ; 78.8)	79/108	73.1	(63.8 ; 81.2)
Unsolicited non-serious AR	128/696	18.4	(15.6 ; 21.5)	128/706	18.1	(15.4 ; 21.2)	10/112	8.9	(4.4 ; 15.8)	17/108	15.7	(9.4 ; 24.0)
Unsolicited non-serious injection site AR related to MenACYW or Nimenrix	84/696	12.1	(9.7 ; 14.7)	74/706	10.5	(8.3 ; 13.0)	6/112	5.4	(2.0 ; 11.3)	13/108	12.0	(6.6 ; 19.7)
Unsolicited non-serious injection site AR related to DTaP-IPV-HB-Hib	158/696	22.7	(19.6 ; 26.0)	142/706	20.1	(17.2 ; 23.3)	5/112	4.5	(1.5 ; 10.1)	4/108	3.7	(1.0 ; 9.2)
Unsolicited non-serious injection site AR related to Prevenar 13 or Synflorix	156/696	22.4	(19.4 ; 25.7)	152/706	21.5	(18.6 ; 24.7)	9/112	8.0	(3.7 ; 14.7)	10/108	9.3	(4.5 ; 16.4)
Unsolicited non-serious injection site AR related to M-M-RVAXPRO	29/696	4.2	(2.8 ; 5.9)	32/706	4.5	(3.1 ; 6.3)	4/112	3.6	(1.0 ; 8.9)	5/108	4.6	(1.5 ; 10.5)
Unsolicited non-serious systemic AE	406/696	58.3	(54.6 ; 62.0)	428/706	60.6	(56.9 ; 64.2)	74/112	66.1	(56.5 ; 74.7)	77/108	71.3	(61.8 ; 79.6)
Unsolicited non-serious systemic AR	56/696	8.0	(6.1 ; 10.3)	63/706	8.9	(6.9 ; 11.3)	4/112	3.6	(1.0 ; 8.9)	4/108	3.7	(1.0 ; 9.2)
AE leading to study discontinuation	0/696	0	(0 ; 0.5)	0/706	0	(0 ; 0.5)	0/112	0	(0 ; 3.2)	0/108	0	(0 ; 3.4)
SAE	18/696	2.6	(1.5 ; 4.1)	16/706	2.3	(1.3 ; 3.7)	2/112	1.8	(0.2 ; 6.3)	1/108	0.9	(0 ; 5.1)
Related SAE	0/696	0	(0 ; 0.5)	0/706	0	(0 ; 0.5)	0/112	0	(0 ; 3.2)	0/108	0	(0 ; 3.4)
Death	0/696	0	(0 ; 0.5)	0/706	0	(0 ; 0.5)	0/112	0	(0 ; 3.2)	0/108	0	(0 ; 3.4)
AESI	1/696	0.1	(0 ; 0.8)	0/706	0	(0 ; 0.5)	0/112	0	(0 ; 3.2)	0/108	0	(0 ; 3.4)
During the study												
SAE	51/696	7.3	(5.5 ; 9.5)	57/706	8.1	(6.2 ; 10.3)	8/112	7.1	(3.1 ; 13.6)	3/108	2.8	(0.6 ; 7.9)
Related SAE	0/696	0	(0 ; 0.5)	0/706	0	(0 ; 0.5)	0/112	0	(0 ; 3.2)	0/108	0	(0 ; 3.4)
Death	0/696	0	(0 ; 0.5)	0/706	0	(0 ; 0.5)	0/112	0	(0 ; 3.2)	0/108	0	(0 ; 3.4)
AESI	3/696	0.4	(0.1 ; 1.3)	3/706	0.4	(0.1 ; 1.2)	0/112	0	(0 ; 3.2)	0/108	0	(0 ; 3.4)

n: number of subjects experiencing the endpoint listed in the first column. M: number of subjects with available data for the relevant endpoint. Percentages are based on M.
N: number of subjects in overall safety analysis set for any dose. "Immediate unsolicited AE" is collected only for immediate unsolicited systemic AEs.
"Unsolicited non-serious AE" includes any unsolicited AE that is non-serious. "Unsolicited AE" also includes immediate and serious unsolicited AEs. AESI: adverse events of special interest.
AR: Reactions related to study vaccine (MenACYW/Nimenrix ®); Unsolicited injection site reactions related to NIMP (routine vaccines) are reported separately.
Group 1: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 2: Nimenrix ® conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12 to 18 months of age.
Group 3: MenACYW conjugate vaccine and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.
Group 4: MenACYW conjugate vaccine administered at 2, 4, 6 and 12 to 18 months of age. Routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12 to 18 months of age.
Study: MET58 Program: t08193to197.sas Datasets=ADSL ADAE ADRC Output: PRODOPS/SP0047/MET58/CSR_01/REPORT/OUTPUT/T08193_i.rtf (26AUG2024 11:33)
Source: Section 8, Table 8.193

Table 94: Summary of solicited reactions and SAEs between MenACYW conjugate vaccine and Nimenrix – overall SafAS post any dose

	MenACYW conjugate vaccine + routine pediatric vaccines (Group 1) (N=696)			Nimenrix + routine pediatric vaccines (Group 2) (N=706)			Group 1 - Group 2	
Subjects experiencing at least one:	n/M	%	(95% CI)	n/M	%	(95% CI)	Difference (%)	(95% CI)
Within 7 days after any dose								
Solicited injection site reactions	628/696	90.2	(87.8 ; 92.3)	632/705	89.6	(87.2 ; 91.8)	0.58	(-2.59 ; 3.75)
Grade 3 solicited injection site reactions	103/696	14.8	(12.2 ; 17.7)	102/705	14.5	(12.0 ; 17.3)	0.33	(-3.38 ; 4.04)
Solicited injection reactions at site of MenACYW conjugate vaccine / Nimenrix	494/696	71.0	(67.4 ; 74.3)	476/705	67.5	(63.9 ; 71.0)	3.46	(-1.37 ; 8.27)
Grade 3 solicited injection reactions at site of MenACYW conjugate vaccine / Nimenrix	31/696	4.5	(3.0 ; 6.3)	35/705	5.0	(3.5 ; 6.8)	-0.51	(-2.78 ; 1.75)
Solicited systemic reactions	661/696	95.0	(93.1 ; 96.5)	659/705	93.5	(91.4 ; 95.2)	1.50	(-0.97 ; 3.99)
Grade 3 solicited systemic reactions	126/696	18.1	(15.3 ; 21.2)	124/705	17.6	(14.8 ; 20.6)	0.51	(-3.50 ; 4.53)
During the study								
SAE	51/696	7.3	(5.5 ; 9.5)	57/706	8.1	(6.2 ; 10.3)	-0.75	(-3.57 ; 2.07)

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 post any dose.
Percentages are based on M; Contributing study: MET58.
95% CI of the single proportion calculated from the exact binomial method.
95% CI of the difference calculated from the Wilson Score method without continuity correction.
Study: OVERALL Program: t01001.sas Datasets=ADSL ADRC ADAE Output: PRODOPS/SP0047/OVERALL/BRA_2025/REPORT/OUTPUT/T01001_x.pdf (10MAR2025 4:15)

Immediate unsolicited adverse events and adverse reactions

After any dose administered in infancy from 6 weeks to less than 12 months of age – SafAS2

A total of 7 participants (0.1%) who received MenACYW conjugate vaccine and 1 participant (<0.1%) who received Menveo experienced at least 1 immediate unsolicited AE within 30 minutes after receiving any vaccine injection. Two participants (<0.1%) who received MenACYW conjugate vaccine experienced at least 1 immediate unsolicited AR within 30 minutes after receiving any vaccine injection. None of the participants who received Menveo reported any immediate unsolicited AR within 30 minutes after receiving any vaccine injection. None of the participants who received Nimenrix experienced any immediate unsolicited AE and AR within 30 minutes after receiving any vaccine injection.

After booster dose administered at 12 to 18 months of age – SafAS6

A total of 4 participants (<0.1%) who received MenACYW conjugate vaccine, 2 participants (0.1%) who received Menveo experienced at least 1 immediate unsolicited AE within 30 minutes after receiving booster vaccination. Three participants (<0.1%) who received MenACYW conjugate vaccine and 1 participant (<0.1%) who received Menveo experienced at least 1 immediate unsolicited AR within 30 minutes after receiving booster vaccination. None of the participants who received Nimenrix experienced any immediate unsolicited AE and AR within 30 minutes after receiving any vaccine injection.

After any dose administered from 6 weeks to 18 months of age – SafAS1

A total of 11 participants (0.2%) who received MenACYW conjugate vaccine, 3 participants (0.1%) who received Menveo experienced at least 1 immediate unsolicited AE within 30 minutes of receiving any vaccine injection. Five participants (<0.1%) who received MenACYW conjugate vaccine and 1 participant (<0.1%) who received Menveo experienced at least 1 immediate unsolicited AR within 30

minutes of receiving any vaccine injection. None of the participants who received Nimenrix experienced any immediate unsolicited AE and AR within 30 minutes of receiving any vaccine injection.

Solicited injection site reactions

After any dose administered in infancy from 6 weeks to less than 12 months of age – SafAS2

The most commonly reported solicited injection site reaction at the MenACYW conjugate vaccine, Menveo or Nimenrix injection site was tenderness experienced by 55.6% participants who received the MenACYW conjugate vaccine, 59.4% participants who received Menveo, and 37.9% participants who received Nimenrix. Erythema and swelling were experienced less frequently. The majority of reactions at the injection site were of Grade 1 or Grade 2 intensity; most started and resolved within 3 days of vaccination The percentage of participants who experienced at least 1 Grade 3 injection site reaction after vaccination was 5.4% in participants who received the MenACYW conjugate vaccine, 6.6% in participants who received Menveo, and 2.6% participants who received Nimenrix.

Table 95: Solicited reactions within 7 days after any vaccine injections, by maximum intensity – SafAS2 (Rapp assessor note: extract from Table 11 from the summary of clinical safety focussed on meningococcal vaccine injection site reactions)

		MenACYW + routine paediatric vaccines (N=6060)			Menveo + routine paediatric vaccines (N=2024)			Nimenrix + routine paediatric vaccines (N=706)		
Participants experiencing at least one:	**Maximum intensity**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
MenACYW or Menveo or Nimenrix										
Injection site Tenderness	Any	3269/5884	55.6	(54.3 ; 56.8)	1152/1941	59.4	(57.1 ; 61.5)	267/705	37.9	(34.3 ; 41.6)
	Grade 1	1984/5884	33.7	(32.5 ; 34.9)	662/1941	34.1	(32.0 ; 36.3)	183/705	26.0	(22.8 ; 29.4)
	Grade 2	975/5884	16.6	(15.6 ; 17.5)	365/1941	18.8	(17.1 ; 20.6)	69/705	9.8	(7.7 ; 12.2)
	Grade 3	310/5884	5.3	(4.7 ; 5.9)	125/1941	6.4	(5.4 ; 7.6)	15/705	2.1	(1.2 ; 3.5)
Injection site Erythema	Any	1819/5883	30.9	(29.7 ; 32.1)	545/1941	28.1	(26.1 ; 30.1)	176/705	25.0	(21.8 ; 28.3)
	Grade 1	1757/5883	29.9	(28.7 ; 31.1)	526/1941	27.1	(25.1 ; 29.1)	167/705	23.7	(20.6 ; 27.0)
	Grade 2	53/5883	0.9	(0.7 ; 1.2)	15/1941	0.8	(0.4 ; 1.3)	8/705	1.1	(0.5 ; 2.2)
	Grade 3	9/5883	0.2	(0.1 ; 0.3)	4/1941	0.2	(0.1 ; 0.5)	1/705	0.1	(0 ; 0.8)
Injection site Swelling	Any	1133/5881	19.3	(18.3 ; 20.3)	359/1942	18.5	(16.8 ; 20.3)	85/705	12.1	(9.7 ; 14.7)
	Grade 1	1081/5881	18.4	(17.4 ; 19.4)	342/1942	17.6	(15.9 ; 19.4)	77/705	10.9	(8.7 ; 13.5)
	Grade 2	42/5881	0.7	(0.5 ; 1.0)	14/1942	0.7	(0.4 ; 1.2)	6/705	0.9	(0.3 ; 1.8)
	Grade 3	10/5881	0.2	(0.1 ; 0.3)	3/1942	0.2	(0 ; 0.5)	2/705	0.3	(0 ; 1.0)

n: number of participants experiencing the endpoint; M: number of participants with available data for the relevant endpoint
N: number of participants in safety analysis set post any dose for infant vaccination; Percentages are based on M.
Contributing studies: MET33, MET41, MET42, MET52, MET58 and Group 1 and Group 2 of MET61
SafAS2 was defined as those participants who received at least 1 dose of the study vaccines from 2 to 7 months of age and had any safety data available.
Source: Modified from 5.3.5.3 Integrated Safety Summary Report Table 4.1.2.7

After booster dose administered at 12 to 18 months of age – SafAS6

The most commonly reported solicited injection site reaction at the MenACYW conjugate vaccine, Menveo or Nimenrix injection site was tenderness experienced by 42.5% participants who received the MenACYW conjugate vaccine, 41.7% participants who received Menveo, and 45.6% participants who received Nimenrix. Erythema and swelling were experienced less frequently. The majority of reactions at the injection site were of Grade 1 or Grade 2 intensity; most started and resolved within 3 days of vaccination. The percentage of participants who experienced at least 1 Grade 3 injection site reaction after vaccination was 2.9% in participants who received the MenACYW conjugate vaccine, 2.1% in participants who received Menveo, and 2.5% participants who received Nimenrix.

Table 96: Solicited reactions within 7 days after vaccine injection at 12 to 18 months of age, by maximum intensity -SafAS6 (Rapp assessor note: extract from Table 16 from the summary of clinical safety focussed on meningococcal vaccine injection site reactions)

		MenACYW + routine paediatric vaccines (N=5373)			Menveo + routine paediatric vaccines (N=1724)			Nimenrix + routine paediatric vaccines (N=696)		
Participants experiencing at least one:	**Maximum intensity**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
MenACYW or Menveo or Nimenrix										
Injection site Tenderness	Any	2190/5147	42.5	(41.2 ; 43.9)	667/1600	41.7	(39.3 ; 44.1)	315/691	45.6	(41.8 ; 49.4)
	Grade 1	1534/5147	29.8	(28.6 ; 31.1)	484/1600	30.3	(28.0 ; 32.6)	213/691	30.8	(27.4 ; 34.4)
	Grade 2	542/5147	10.5	(9.7 ; 11.4)	153/1600	9.6	(8.2 ; 11.1)	87/691	12.6	(10.2 ; 15.3)
	Grade 3	114/5147	2.2	(1.8 ; 2.7)	30/1600	1.9	(1.3 ; 2.7)	15/691	2.2	(1.2 ; 3.6)
Injection site Erythema	Any	1343/5146	26.1	(24.9 ; 27.3)	333/1599	20.8	(18.9 ; 22.9)	182/691	26.3	(23.1 ; 29.8)
	Grade 1	1264/5146	24.6	(23.4 ; 25.8)	320/1599	20.0	(18.1 ; 22.1)	173/691	25.0	(21.8 ; 28.4)
	Grade 2	45/5146	0.9	(0.6 ; 1.2)	9/1599	0.6	(0.3 ; 1.1)	6/691	0.9	(0.3 ; 1.9)
	Grade 3	34/5146	0.7	(0.5 ; 0.9)	4/1599	0.3	(0.1 ; 0.6)	3/691	0.4	(0.1 ; 1.3)
Injection site Swelling	Any	745/5144	14.5	(13.5 ; 15.5)	212/1598	13.3	(11.6 ; 15.0)	98/691	14.2	(11.7 ; 17.0)
	Grade 1	710/5144	13.8	(12.9 ; 14.8)	207/1598	13.0	(11.3 ; 14.7)	94/691	13.6	(11.1 ; 16.4)
	Grade 2	18/5144	0.3	(0.2 ; 0.6)	3/1598	0.2	(0 ; 0.5)	2/691	0.3	(0 ; 1.0)
	Grade 3	17/5144	0.3	(0.2 ; 0.5)	2/1598	0.1	(0 ; 0.5)	2/691	0.3	(0 ; 1.0)

n: number of participants experiencing the endpoint; M: number of participants with available data for the relevant endpoint
N: number of participants in safety analysis set post booster dose; Percentages are based on M.
Contributing studies: MET33, MET41, MET42, MET52, MET58 and Group 1 and Group 2 of MET61
*MMR refers to M-M-RII, M-M-RVAXPRO and locally licensed MMR or MM+R vaccines that are allowed to be administered in the included studies
SafAS6 was defined as those participants who received the booster dose of the study vaccine and had any safety data available
Source: Modified from 5.3.5.3 Integrated Safety Summary Report Table 5.2.7

Descriptive comparison solicited reactions in infants 6 weeks to less than 12 months of age with toddler 12 months to 18 months of age

Table 97: Summary of solicited reactions within 7 days after any vaccine injections

Participants experiencing at least one:	MenACYW + routine paediatric vaccines	
	6 weeks to <12 months of age (SafAS2) (n=6060)	12-18 months of age (SafAS6) (n=5373)
Solicited reaction	**86.8%**	**74.5%**
Grade 3 solicited reaction	17.2%	10.5%
Solicited injection site reaction	**74.8%**	**62.2%**
Solicited injection site reaction after injection of MenACYW conjugate vaccine	64.3%	50.8%
Grade 3 injection site reaction	8.3%	6.3%
Grade 3 solicited injection site reaction after injection of MenACYW conjugate vaccine	5.4%	2.9%
Solicited systemic reaction	**80.2%**	**63.8%**
Grade 3 systemic reaction	13.0%	6.1%

Source: Modified from 5.3.5.3 Integrated Safety Summary Report Table 4.1.2.4 and Table 5.2.4

After any dose administered 6 weeks to 18 months of age – SafAS1

Table 98: Solicited reactions within 7 days after any vaccine injections, by maximum intensity - SafAS1 (Rapp assessor note: extract from Table 21 from the summary of clinical safety focussed on meningococcal vaccine injection site reactions)

Participants experiencing at least one:	Maximum intensity	MenACYW + routine paediatric vaccines (N=6060) n/M	%	(95% CI)	Menveo + routine paediatric vaccines (N=2024) n/M	%	(95% CI)	Nimenrix + routine paediatric vaccines (N=706) n/M	%	(95% CI)
MenACYW or Menveo or Nimenrix										
Injection site Tenderness	Any	3807/5897	64.6	(63.3 ; 65.8)	1271/1946	65.3	(63.2 ; 67.4)	411/705	58.3	(54.6 ; 62.0)
	Grade 1	2171/5897	36.8	(35.6 ; 38.1)	701/1946	36.0	(33.9 ; 38.2)	253/705	35.9	(32.3 ; 39.6)
	Grade 2	1248/5897	21.2	(20.1 ; 22.2)	428/1946	22.0	(20.2 ; 23.9)	128/705	18.2	(15.4 ; 21.2)
	Grade 3	388/5897	6.6	(6.0 ; 7.2)	142/1946	7.3	(6.2 ; 8.5)	30/705	4.3	(2.9 ; 6.0)
Injection site Erythema	Any	2306/5896	39.1	(37.9 ; 40.4)	645/1946	33.1	(31.1 ; 35.3)	267/705	37.9	(34.3 ; 41.6)
	Grade 1	2167/5896	36.8	(35.5 ; 38.0)	613/1946	31.5	(29.4 ; 33.6)	249/705	35.3	(31.8 ; 39.0)
	Grade 2	96/5896	1.6	(1.3 ; 2.0)	24/1946	1.2	(0.8 ; 1.8)	14/705	2.0	(1.1 ; 3.3)
	Grade 3	43/5896	0.7	(0.5 ; 1.0)	8/1946	0.4	(0.2 ; 0.8)	4/705	0.6	(0.2 ; 1.4)
Injection site Swelling	Any	1504/5893	25.5	(24.4 ; 26.7)	444/1947	22.8	(21.0 ; 24.7)	152/705	21.6	(18.6 ; 24.8)
	Grade 1	1418/5893	24.1	(23.0 ; 25.2)	423/1947	21.7	(19.9 ; 23.6)	140/705	19.9	(17.0 ; 23.0)
	Grade 2	59/5893	1.0	(0.8 ; 1.3)	16/1947	0.8	(0.5 ; 1.3)	8/705	1.1	(0.5 ; 2.2)
	Grade 3	27/5893	0.5	(0.3 ; 0.7)	5/1947	0.3	(0.1 ; 0.6)	4/705	0.6	(0.2 ; 1.4)

n: number of participants experiencing the endpoint; M: number of participants with available data for the relevant endpoint
N: number of participants in safety analysis set post any dose; Percentages are based on M.
Contributing studies: MET33, MET41, MET42, MET52, MET58 and Group 1 and Group 2 of MET61
*MMR refers to M-M-RII, M-M-RVAXPRO and locally licensed MMR or MM+R vaccines that are allowed to be administered in the included studies
SafAS1 was defined as those participants who received at least 1 dose of the study vaccines and had any safety data available

Participants experiencing at least one:	Maximum intensity	MenACYW + routine paediatric vaccines (N=6060) n/M	%	(95% CI)	Menveo + routine paediatric vaccines (N=2024) n/M	%	(95% CI)	Nimenrix + routine paediatric vaccines (N=706) n/M	%	(95% CI)

Source: Modified from 5.3.5.3 Integrated Safety Summary Report Table 3.2.7

Solicited systemic reactions

The percentage of participants who experienced at least 1 **solicited systemic reaction after any vaccine injection** was 83.3% in participants who received MenACYW conjugate vaccine, 79.7% in participants who received Menveo, and 93.5% in participants who received Nimenrix. The percentage of participants who experienced at least 1 Grade 3 solicited systemic reaction after any vaccine injection was 16.3% in participants who received MenACYW conjugate vaccine, 15.6% in participants who received Menveo, and 17.6% in participants who received Nimenrix.

After any dose administered in infancy from 6 weeks to less than 12 months of age – SafAS2

The most commonly reported solicited systemic reaction was irritability experienced by 69.8% participants who received the MenACYW conjugate vaccine, 66.4% participants who received Menveo, and 78.7% participants who received Nimenrix followed by abnormal crying experienced by 60.5% participants who received the MenACYW conjugate vaccine, 57.0% participants who received Menveo, and 73.8% participants who received Nimenrix and drowsiness experienced by 58.4% participants who received the MenACYW conjugate vaccine, 56.3% participants who received Menveo, and 69.5% participants who received Nimenrix.

The percentage of participants who experienced at least 1 Grade 3 systemic reaction after vaccination with MenACYW conjugate vaccine, Menveo or Nimenrix at infancy was 13.0% in participants who received the MenACYW conjugate vaccine, 12.7% in participants who received Menveo, and 11.5% participants who received Nimenrix.

Table 99: Solicited systemic reaction after any vaccine injections, by maximum intensity - SafAS2

Participants experiencing at least one:	Maximum intensity	MenACYW + routine paediatric vaccines (N=6060) n/M	%	(95% CI)	Menveo + routine paediatric vaccines (N=2024) n/M	%	(95% CI)	Nimenrix + routine paediatric vaccines (N=706) n/M	%	(95% CI)
Fever	Any	1443/5813	24.8	(23.7 ; 26.0)	484/1904	25.4	(23.5 ; 27.4)	239/705	33.9	(30.4 ; 37.5)
	Grade 1	937/5813	16.1	(15.2 ; 17.1)	305/1904	16.0	(14.4 ; 17.7)	171/705	24.3	(21.1 ; 27.6)
	Grade 2	452/5813	7.8	(7.1 ; 8.5)	160/1904	8.4	(7.2 ; 9.7)	68/705	9.6	(7.6 ; 12.1)
	Grade 3	54/5813	0.9	(0.7 ; 1.2)	19/1904	1.0	(0.6 ; 1.6)	0/705	0	(0 ; 0.5)
Vomiting	Any	1257/5879	21.4	(20.3 ; 22.5)	345/1944	17.7	(16.1 ; 19.5)	167/705	23.7	(20.6 ; 27.0)
	Grade 1	732/5879	12.5	(11.6 ; 13.3)	204/1944	10.5	(9.2 ; 11.9)	92/705	13.0	(10.7 ; 15.8)
	Grade 2	485/5879	8.2	(7.6 ; 9.0)	128/1944	6.6	(5.5 ; 7.8)	71/705	10.1	(7.9 ; 12.5)
	Grade 3	40/5879	0.7	(0.5 ; 0.9)	13/1944	0.7	(0.4 ; 1.1)	4/705	0.6	(0.2 ; 1.4)
Crying abnormal	Any	3555/5878	60.5	(59.2 ; 61.7)	1108/1944	57.0	(54.8 ; 59.2)	520/705	73.8	(70.3 ; 77.0)

Participants experiencing at least one:	Maximum intensity	MenACYW + routine paediatric vaccines (N=6060) n/M	%	(95% CI)	Menveo + routine paediatric vaccines (N=2024) n/M	%	(95% CI)	Nimenrix + routine paediatric vaccines (N=706) n/M	%	(95% CI)
	Grade 1	1871/5878	31.8	(30.6 ; 33.0)	577/1944	29.7	(27.7 ; 31.8)	237/705	33.6	(30.1 ; 37.2)
	Grade 2	1337/5878	22.7	(21.7 ; 23.8)	438/1944	22.5	(20.7 ; 24.5)	234/705	33.2	(29.7 ; 36.8)
	Grade 3	347/5878	5.9	(5.3 ; 6.5)	93/1944	4.8	(3.9 ; 5.8)	49/705	7.0	(5.2 ; 9.1)
Drowsiness	Any	3433/5878	58.4	(57.1 ; 59.7)	1093/1943	56.3	(54.0 ; 58.5)	490/705	69.5	(66.0 ; 72.9)
	Grade 1	2293/5878	39.0	(37.8 ; 40.3)	684/1943	35.2	(33.1 ; 37.4)	391/705	55.5	(51.7 ; 59.2)
	Grade 2	913/5878	15.5	(14.6 ; 16.5)	314/1943	16.2	(14.6 ; 17.9)	82/705	11.6	(9.4 ; 14.2)
	Grade 3	227/5878	3.9	(3.4 ; 4.4)	95/1943	4.9	(4.0 ; 5.9)	17/705	2.4	(1.4 ; 3.8)
Appetite lost	Any	2104/5878	35.8	(34.6 ; 37.0)	699/1944	36.0	(33.8 ; 38.1)	262/705	37.2	(33.6 ; 40.8)
	Grade 1	1431/5878	24.3	(23.3 ; 25.5)	497/1944	25.6	(23.6 ; 27.6)	194/705	27.5	(24.3 ; 31.0)
	Grade 2	581/5878	9.9	(9.1 ; 10.7)	165/1944	8.5	(7.3 ; 9.8)	62/705	8.8	(6.8 ; 11.1)
	Grade 3	92/5878	1.6	(1.3 ; 1.9)	37/1944	1.9	(1.3 ; 2.6)	6/705	0.9	(0.3 ; 1.8)
Irritability	Any	4102/5878	69.8	(68.6 ; 71.0)	1290/1944	66.4	(64.2 ; 68.5)	555/705	78.7	(75.5 ; 81.7)
	Grade 1	1617/5878	27.5	(26.4 ; 28.7)	540/1944	27.8	(25.8 ; 29.8)	183/705	26.0	(22.8 ; 29.4)
	Grade 2	2027/5878	34.5	(33.3 ; 35.7)	599/1944	30.8	(28.8 ; 32.9)	340/705	48.2	(44.5 ; 52.0)
	Grade 3	458/5878	7.8	(7.1 ; 8.5)	151/1944	7.8	(6.6 ; 9.0)	32/705	4.5	(3.1 ; 6.3)

n: number of participants experiencing the endpoint; M: number of participants with available data for the relevant endpoint
N: number of participants in safety analysis set post any dose for infant vaccination; Percentages are based on M.
Contributing studies: MET33, MET41, MET42, MET52, MET58 and Group 1 and Group 2 of MET61
SafAS2 was defined as those participants who received at least 1 dose of the study vaccines from 2 to 7 months of age and had any safety data available.
Source: Modified from 5.3.5.3 Integrated Safety Summary Report Table 4.1.2.10

After booster dose administered at 12 to 18 months of age – SafAS6

The most commonly reported solicited systemic reaction was irritability experienced by 53.5% participants who received the MenACYW conjugate vaccine, 47.6% participants who received Menveo, and 68.6% participants who received Nimenrix followed by abnormal crying experienced by 40.1% participants who received the MenACYW conjugate vaccine, 34.5% participants who received Menveo, and 62.1% participants who received Nimenrix and drowsiness experienced by 35.9% participants who received the MenACYW conjugate vaccine, 33.0% participants who received Menveo, and 46.1% participants who received Nimenrix.

The percentage of participants who experienced at least 1 Grade 3 systemic reaction after vaccination was 6.1% in participants who received the MenACYW conjugate vaccine, 4.9% in participants who received Menveo, and 8.1% participants who received Nimenrix.

Table 100: Solicited systemic reaction after vaccine injection at 12 to 18 months of age, by maximum intensity - SafAS6

Participants experiencing at least one:	Maximum intensity	MenACYW + routine paediatric vaccines (N=5373) n/M	%	(95% CI)	Menveo + routine paediatric vaccines (N=1724) n/M	%	(95% CI)	Nimenrix + routine paediatric vaccines (N=696) n/M	%	(95% CI)
Fever	Any	803/5019	16.0	(15.0 ; 17.0)	171/1549	11.0	(9.5 ; 12.7)	158/689	22.9	(19.8 ; 26.3)
	Grade 1	526/5019	10.5	(9.6 ; 11.4)	99/1549	6.4	(5.2 ; 7.7)	104/689	15.1	(12.5 ; 18.0)
	Grade 2	234/5019	4.7	(4.1 ; 5.3)	61/1549	3.9	(3.0 ; 5.0)	48/689	7.0	(5.2 ; 9.1)
	Grade 3	43/5019	0.9	(0.6 ; 1.2)	11/1549	0.7	(0.4 ; 1.3)	6/689	0.9	(0.3 ; 1.9)
Vomiting	Any	328/5146	6.4	(5.7 ; 7.1)	72/1600	4.5	(3.5 ; 5.6)	48/690	7.0	(5.2 ; 9.1)
	Grade 1	242/5146	4.7	(4.1 ; 5.3)	52/1600	3.3	(2.4 ; 4.2)	41/690	5.9	(4.3 ; 8.0)
	Grade 2	76/5146	1.5	(1.2 ; 1.8)	17/1600	1.1	(0.6 ; 1.7)	6/690	0.9	(0.3 ; 1.9)
	Grade 3	10/5146	0.2	(0.1 ; 0.4)	3/1600	0.2	(0 ; 0.5)	1/690	0.1	(0 ; 0.8)
Crying abnormal	Any	2063/5144	40.1	(38.8 ; 41.5)	552/1600	34.5	(32.2 ; 36.9)	429/691	62.1	(58.3 ; 65.7)
	Grade 1	1304/5144	25.3	(24.2 ; 26.6)	367/1600	22.9	(20.9 ; 25.1)	249/691	36.0	(32.4 ; 39.7)
	Grade 2	637/5144	12.4	(11.5 ; 13.3)	152/1600	9.5	(8.1 ; 11.0)	150/691	21.7	(18.7 ; 25.0)
	Grade 3	122/5144	2.4	(2.0 ; 2.8)	33/1600	2.1	(1.4 ; 2.9)	30/691	4.3	(2.9 ; 6.1)
Drowsiness	Any	1845/5143	35.9	(34.6 ; 37.2)	528/1600	33.0	(30.7 ; 35.4)	318/690	46.1	(42.3 ; 49.9)
	Grade 1	1439/5143	28.0	(26.8 ; 29.2)	407/1600	25.4	(23.3 ; 27.6)	272/690	39.4	(35.8 ; 43.2)
	Grade 2	328/5143	6.4	(5.7 ; 7.1)	100/1600	6.3	(5.1 ; 7.5)	44/690	6.4	(4.7 ; 8.5)
	Grade 3	78/5143	1.5	(1.2 ; 1.9)	21/1600	1.3	(0.8 ; 2.0)	2/690	0.3	(0 ; 1.0)
Appetite lost	Any	1341/5144	26.1	(24.9 ; 27.3)	353/1599	22.1	(20.1 ; 24.2)	232/691	33.6	(30.1 ; 37.2)
	Grade 1	1002/5144	19.5	(18.4 ; 20.6)	272/1599	17.0	(15.2 ; 18.9)	176/691	25.5	(22.3 ; 28.9)
	Grade 2	270/5144	5.2	(4.7 ; 5.9)	62/1599	3.9	(3.0 ; 4.9)	48/691	6.9	(5.2 ; 9.1)
	Grade 3	69/5144	1.3	(1.0 ; 1.7)	19/1599	1.2	(0.7 ; 1.8)	8/691	1.2	(0.5 ; 2.3)
Irritability	Any	2755/5145	53.5	(52.2 ; 54.9)	762/1600	47.6	(45.2 ; 50.1)	474/691	68.6	(65.0 ; 72.0)
	Grade 1	1449/5145	28.2	(26.9 ; 29.4)	427/1600	26.7	(24.5 ; 28.9)	225/691	32.6	(29.1 ; 36.2)
	Grade 2	1114/5145	21.7	(20.5 ; 22.8)	290/1600	18.1	(16.3 ; 20.1)	227/691	32.9	(29.4 ; 36.5)
	Grade 3	192/5145	3.7	(3.2 ; 4.3)	45/1600	2.8	(2.1 ; 3.7)	22/691	3.2	(2.0 ; 4.8)

n: number of participants experiencing the endpoint; M: number of participants with available data for the relevant endpoint
N: number of participants in safety analysis set post booster dose; Percentages are based on M.
Contributing studies: MET33, MET41, MET42, MET52, MET58 and Group 1 and Group 2 of MET61
SafAS6 was defined as those participants who received the booster dose of the study vaccine and had any safety data available
Source: Modified from 5.3.5.3 Integrated Safety Summary Report Table 5.2.10

Descriptive comparison solicited reactions in infants 6 weeks to less than 12 months of age with toddler 12 months to 18 months of age

See *Table 97*.

After any dose administered 6 weeks to 18 months of age – SafAS1

Table 101: Solicited systemic reaction after any vaccine injections, by maximum intensity (6 weeks to 18 months of age) - SafAS1

		MenACYW + routine paediatric vaccines (N=6060)			Menveo + routine paediatric vaccines (N=2024)			Nimenrix + routine paediatric vaccines (N=706)		
Participants experiencing at least one:	**Maximum intensity**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Fever	Any	1878/5829	32.2	(31.0 ; 33.4)	571/1913	29.8	(27.8 ; 32.0)	312/705	44.3	(40.5 ; 48.0)
	Grade 1	1143/5829	19.6	(18.6 ; 20.7)	332/1913	17.4	(15.7 ; 19.1)	201/705	28.5	(25.2 ; 32.0)
	Grade 2	641/5829	11.0	(10.2 ; 11.8)	210/1913	11.0	(9.6 ; 12.5)	105/705	14.9	(12.3 ; 17.7)
	Grade 3	94/5829	1.6	(1.3 ; 2.0)	29/1913	1.5	(1.0 ; 2.2)	6/705	0.9	(0.3 ; 1.8)
Vomiting	Any	1446/5893	24.5	(23.4 ; 25.7)	389/1948	20.0	(18.2 ; 21.8)	193/705	27.4	(24.1 ; 30.8)
	Grade 1	854/5893	14.5	(13.6 ; 15.4)	230/1948	11.8	(10.4 ; 13.3)	114/705	16.2	(13.5 ; 19.1)
	Grade 2	542/5893	9.2	(8.5 ; 10.0)	143/1948	7.3	(6.2 ; 8.6)	74/705	10.5	(8.3 ; 13.0)
	Grade 3	50/5893	0.8	(0.6 ; 1.1)	16/1948	0.8	(0.5 ; 1.3)	5/705	0.7	(0.2 ; 1.6)
Crying abnormal	Any	3902/5893	66.2	(65.0 ; 67.4)	1194/1948	61.3	(59.1 ; 63.5)	579/705	82.1	(79.1 ; 84.9)
	Grade 1	1862/5893	31.6	(30.4 ; 32.8)	594/1948	30.5	(28.5 ; 32.6)	220/705	31.2	(27.8 ; 34.8)
	Grade 2	1613/5893	27.4	(26.2 ; 28.5)	482/1948	24.7	(22.8 ; 26.7)	287/705	40.7	(37.1 ; 44.4)
	Grade 3	427/5893	7.2	(6.6 ; 7.9)	118/1948	6.1	(5.0 ; 7.2)	72/705	10.2	(8.1 ; 12.7)
Drowsiness	Any	3709/5891	63.0	(61.7 ; 64.2)	1168/1947	60.0	(57.8 ; 62.2)	545/705	77.3	(74.0 ; 80.3)
	Grade 1	2371/5891	40.2	(39.0 ; 41.5)	703/1947	36.1	(34.0 ; 38.3)	415/705	58.9	(55.1 ; 62.5)
	Grade 2	1055/5891	17.9	(16.9 ; 18.9)	355/1947	18.2	(16.5 ; 20.0)	111/705	15.7	(13.1 ; 18.6)
	Grade 3	283/5891	4.8	(4.3 ; 5.4)	110/1947	5.6	(4.7 ; 6.8)	19/705	2.7	(1.6 ; 4.2)
Appetite lost	Any	2678/5892	45.5	(44.2 ; 46.7)	827/1948	42.5	(40.2 ; 44.7)	372/705	52.8	(49.0 ; 56.5)
	Grade 1	1769/5892	30.0	(28.9 ; 31.2)	566/1948	29.1	(27.0 ; 31.1)	257/705	36.5	(32.9 ; 40.1)
	Grade 2	754/5892	12.8	(12.0 ; 13.7)	210/1948	10.8	(9.4 ; 12.2)	102/705	14.5	(12.0 ; 17.3)
	Grade 3	155/5892	2.6	(2.2 ; 3.1)	51/1948	2.6	(2.0 ; 3.4)	13/705	1.8	(1.0 ; 3.1)
Irritability	Any	4395/5892	74.6	(73.5 ; 75.7)	1366/1948	70.1	(68.0 ; 72.1)	607/705	86.1	(83.3 ; 88.6)

Participants experiencing at least one:	Maximum intensity	MenACYW + routine paediatric vaccines (N=6060) n/M	%	(95% CI)	Menveo + routine paediatric vaccines (N=2024) n/M	%	(95% CI)	Nimenrix + routine paediatric vaccines (N=706) n/M	%	(95% CI)
	Grade 1	1507/5892	25.6	(24.5 ; 26.7)	525/1948	27.0	(25.0 ; 29.0)	163/705	23.1	(20.1 ; 26.4)
	Grade 2	2300/5892	39.0	(37.8 ; 40.3)	653/1948	33.5	(31.4 ; 35.7)	394/705	55.9	(52.1 ; 59.6)
	Grade 3	588/5892	10.0	(9.2 ; 10.8)	188/1948	9.7	(8.4 ; 11.0)	50/705	7.1	(5.3 ; 9.2)

n: number of participants experiencing the endpoint; M: number of participants with available data for the relevant endpoint
N: number of participants in safety analysis set post any dose; Percentages are based on M.
Contributing studies: MET33, MET41, MET42, MET52, MET58 and Group 1 and Group 2 of MET61
SafAS1 was defined as those participants who received at least 1 dose of the study vaccines and had any safety data available
Source: Modified from 5.3.5.3 Integrated Safety Summary Report Table 3.2.10

Unsolicited non-serious adverse events and adverse reactions

Adverse events

After any dose administered in infancy from 6 weeks to less than 12 months of age – SafAS2

The percentage of participants reporting at least 1 unsolicited AE within 30 days of **any vaccine injection at infancy** was 48.8% in participants who received MenACYW conjugate vaccine, 46.8% in participants who received Menveo, and 51.4% in participants who received Nimenrix. The most frequently reported unsolicited AE was in the System Organ Class (SOC) "Infections and Infestations" experienced by 26.8% of participants who received MenACYW conjugate vaccine, 26.9% of participants who received Menveo, and 18.6% of participants who received Nimenrix. The most frequently reported unsolicited AE in this SOC was upper respiratory tract infection experienced by 8.8% of participants who received MenACYW conjugate vaccine, 9.9% of participants who received Menveo, and 4.4% of participants who received Nimenrix.

Most of the unsolicited AEs were of Grade 1 or Grade 2 intensity, started during the time period Day 0 to Day 3 and ≥ 15 days and resolved after 8 days or more. The percentage of participants with Grade 3 unsolicited AEs within 30 days of any vaccine injection was 3.1% in participants who received MenACYW conjugate vaccine, 2.3% in participants who received Menveo, and 2.3% in participants who received Nimenrix.

After booster dose administered at 12 to 18 months of age – SafAS6

The percentage of participants experiencing at least 1 **unsolicited AE within 30 days after booster** vaccination was 37.0% in participants who received MenACYW conjugate vaccine, 28.5% in participants who received Menveo, and 49.1% in participants who received Nimenrix. The most frequently reported unsolicited AE was in the SOC "Infections and Infestations" experienced by 18.1% of participants who received MenACYW conjugate vaccine, 13.6% of participants who received Menveo, and 23.3% of participants who received Nimenrix. The most frequently reported unsolicited AE in this SOC was upper respiratory tract infection experienced by 3.1% of participants who received MenACYW conjugate vaccine, 3.5% of participants who received Menveo, and 5.5% of participants who received Nimenrix.

Table 102: Unsolicited AEs within 30 days after any vaccine injections, by system organ class

	MenACYW + routine paediatric vaccines	
Participants experiencing at least one:	**6 weeks to <12 months of age (SafAS2) (n=6060)**	**12-18 months of age (SafAS6) (n=5373)**
Unsolicited AEs	48.8%	37.0%

	MenACYW + routine paediatric vaccines	
Participants experiencing at least one:	**6 weeks to <12 months of age (SafAS2) (n=6060)**	**12-18 months of age (SafAS6) (n=5373)**
Infections and infestations	26.8%	18.1%
General disorder and administration site conditions	15.5%	13.5%
Gastrointestinal disorder	14.6%	9.4%
Skin and subcutaneous tissue disorders	8.2%	4.7%
Respiratory, thoracic and mediastinal disorders	6.9%	2.9%
Injury, poisoning and procedural complications	1.5%	1.3%
Metabolism and nutrition disorders	1.1%	0.2%
Congenital, familial and genetic disorders	1.0%	0.1%
Eye disorders	0.9%	0.3%
Nervous system disorders	0.7%	0.4%
Ear and labyrinth disorders	0.7%	0.5%
Psychiatric disorders	0.7%	0.3%
Immune system disorders	0.6%	0.4%
Musculoskeletal and connective disorders	0.6%	0.2%
Investigations	0.6%	0.4%
Reproductive system and breast disorders	0.3%	0.2%
Blood and lymphatic system disorders	0.2%	0.4%
Neoplasm, benign, malignant and unspecified (incl. cysts and polyps)	<0.1%	<0.1%
Renal and urinary disorders	<0.1%	<0.1%
Vascular disorder	<0.1%	<0.1%
Cardiac disorder	<0.1%	0%
Endocrine disorders	<0.1%	0%
Pregnancy, puerperium and perinatal conditions	<0.1%	0%
Hepatobiliary disorders	0%	0%

Source: Modified from 5.3.5.3 Integrated Safety Summary Report Table 4.1.2.12 and Table 5.2.12

After any dose administered 6 weeks to 18 months of age – SafAS1

The percentage of participants experiencing at least 1 unsolicited AE within 30 days of **any vaccine injection** was 59.5% in participants who received MenACYW conjugate vaccine, 54.1% in participants who received Menveo, and 68.0% in participants who received Nimenrix. The most frequently reported unsolicited AE was in the SOC "Infections and Infestations" experienced by 36.6% of participants who received MenACYW conjugate vaccine, 33.1% of participants who received Menveo, and 35.8% of participants who received Nimenrix. The most frequently reported unsolicited AE in this SOC was upper respiratory tract infection experienced by 10.9% of participants who received MenACYW conjugate vaccine, 12.3% of participants who received Menveo, and 8.6% of participants who received Nimenrix.

Refer to Table 87.

Adverse reactions

After any dose administered in infancy from 6 weeks to less than 12 months of age – SafAS2

The percentage of participants reporting at least 1 unsolicited AR within 30 **days of any vaccine injection at infancy** was 6.0% in participants who received MenACYW conjugate vaccine, 4.9% in participants who received Menveo, and 9.8% in participants who received Nimenrix. The most frequently reported unsolicited AR was in the SOC "General disorders and administration site conditions" experienced by 5.2% of participants who received MenACYW conjugate vaccine, 4.5% of participants who received Menveo, and 6.1% of participants who received Nimenrix. The most frequently reported unsolicited AR in this SOC was injection site bruising experienced by 4.1% of participants who received MenACYW conjugate vaccine, 4.0% of participants who received Menveo, and 3.4% of participants who received Nimenrix.

Most of the unsolicited ARs were of Grade 1 intensity, started during the time period Day 0 to Day 3 and resolved within 3 to 7 days of vaccination. The percentage of participants with Grade 3 unsolicited ARs within 30 days of any vaccine injection at infancy was 0.2% in participants who received MenACYW conjugate vaccine and 0.2% in participants who received Menveo. There were no Grade 3 unsolicited ARs experienced by participants who received Nimenrix.

After booster dose administered at 12 to 18 months of age – SafAS6

The percentage of participants experiencing at least 1 unsolicited AR within 30 days of **booster vaccination** was 4.9% in participants who received MenACYW conjugate vaccine, 2.9% in participants who received Menveo, and 10.3% in participants who received Nimenrix. The most frequently reported unsolicited AE was in the SOC "General disorders and administration site conditions" experienced by 4.1% of participants who received MenACYW conjugate vaccine, 2.6% of participants who received Menveo, and 7.2% of participants who received Nimenrix. The most frequently reported unsolicited AR in this SOC was injection site bruising experienced by 2.9% of participants who received MenACYW conjugate vaccine, 2.1% of participants who received Menveo, and 2.6% of participants who received Nimenrix.

Most of the unsolicited ARs were of Grade 1 intensity, started during the time period Day 0 to Day 3 and resolved within 3 to 7 days of vaccination. The percentage of participants with Grade 3 unsolicited ARs within 30 days after booster vaccination was 0.1% in participants who received MenACYW conjugate vaccine, <0.1% in participants who received Menveo, and 0.4% in participants who received Nimenrix.

Table 103: Unsolicited ARs within 30 days after any vaccine injections, by system organ class

	MenACYW + routine paediatric vaccines	
Participants experiencing at least one:	**6 weeks to <12 months of age (SafAS2) (n=6060)**	**12-18 months of age (SafAS6) (n=5373)**
Unsolicited ARs	6.0%	4.9%
Infections and infestations	0.2%	0.1%
General disorder and administration site conditions	5.2%	4.1%
Gastrointestinal disorder	0.5%	0.2%
Skin and subcutaneous tissue disorders	0.2%	0.4%
Respiratory, thoracic and mediastinal disorders	<0.1%	<0.1%
Injury, poisoning and procedural complications	0%	<0.1%
Metabolism and nutrition disorders	0%	0%
Congenital, familial and genetic disorders	0%	0%
Eye disorders	<0.1%	<0.1%
Nervous system disorders	<0.1%	<0.1%

	MenACYW + routine paediatric vaccines	
Participants experiencing at least one:	**6 weeks to <12 months of age (SafAS2) (n=6060)**	**12-18 months of age (SafAS6) (n=5373)**
Ear and labyrinth disorders	0%	<0.1%
Psychiatric disorders	<0.1%	<0.1%
Immune system disorders	0%	<0.1%
Musculoskeletal and connective disorders	0%	<0.1%
Investigations	0%	<0.1%
Reproductive system and breast disorders	0%	<0.1%
Blood and lymphatic system disorders	0%	<0.1%
Neoplasm, benign, malignant and unspecified (incl. cysts and polyps)	0%	0%
Renal and urinary disorders	0%	0%
Vascular disorder	<0.1%	0%
Cardiac disorder	0%	0%
Endocrine disorders	0%	0%
Pregnancy, puerperium and perinatal conditions	0%	0%
Hepatobiliary disorders	0%	0%

Source: Modified from 5.3.5.3 Integrated Safety Summary Report Table 4.1.2.13 and Table 5.2.13

After any dose administered 6 weeks to 18 months of age – SafAS1

The percentage of participants experiencing at least 1 unsolicited AR within 30 days of **any vaccine injection** was 9.3% in participants who received MenACYW conjugate vaccine, 6.9% in participants who received Menveo, and 18.1% in participants who received Nimenrix. The most frequently reported unsolicited AR was in the SOC "General disorders and administration site conditions" experienced by 8.0% of participants who received MenACYW conjugate vaccine, 6.3% of participants who received Menveo, and 12.3% of participants who received Nimenrix.

The most frequently reported unsolicited AR in this SOC was injection site bruising experienced by 6.1% of participants who received MenACYW conjugate vaccine, 5.4% of participants who received Menveo, and 5.9% of participants who received Nimenrix.

Most of the unsolicited ARs were of Grade 1 intensity, started during the time period Day 0 to Day 3 and resolved within 1 to 7 days of vaccination. The percentage of participants with Grade 3 unsolicited ARs within 30 days of any vaccine injection was 0.4% in participants who received MenACYW conjugate vaccine, 0.3% in participants who received Menveo, and 0.4% in participants who received Nimenrix.

Serious adverse event/deaths/other significant events

Serious adverse events – integrated summary

After any dose administered 6 weeks to 18 months of age – SafAS1

The percentage of participants with at least 1 SAE within 7 days of any vaccine injection was 0.6% in participants who received MenACYW conjugate vaccine, 0.3% in participants who received Menveo, and 0.3% in participants who received Nimenrix. The percentage of participants with at least 1 SAE within 30 days of any vaccine injection was 2.0% in participants who received MenACYW conjugate vaccine, 1.0% in participants who received Menveo, and 2.3% in participants who received Nimenrix. The percentage of participants with at least 1 SAE during the 6-month follow-up period after any

vaccine injection was 1.3% in participants who received MenACYW conjugate vaccine and 1.0% in participants who received Menveo.

Table 104: Overview of SAEs (6 weeks to 18 months of age) - SafAS1

	MenACYW + routine paediatric vaccines (N=6060)							
	All SAEs				Related SAEs			
Participants experiencing at least one SAE:	**n/M**	**%**	**(95% CI)**	**n SAEs**	**n/M**	**%**	**(95% CI)**	**n SAEs**
Within 7 days after any vaccine injections	36/6060	0.6	(0.4 ; 0.8)	38	2/6060	<0.1	(0 ; 0.1)	2
Within 30 days after any vaccine injections	120/6060	2.0	(1.6 ; 2.4)	141	3/6060	<0.1	(0 ; 0.1)	3
During 6-month follow-up period *	55/4177	1.3	(1.0 ; 1.7)	69	0/4177	0	(0 ; 0.1)	0
During the study	291/6060	4.8	(4.3 ; 5.4)	386	3/6060	<0.1	(0 ; 0.1)	3

	Menveo + routine paediatric vaccines (N=2024)							
	All SAEs				Related SAEs			
Participants experiencing at least one SAE:	**n/M**	**%**	**(95% CI)**	**n SAEs**	**n/M**	**%**	**(95% CI)**	**n SAEs**
Within 7 days after any vaccine injections	7/2024	0.3	(0.1 ; 0.7)	7	1/2024	<0.1	(0 ; 0.3)	1
Within 30 days after any vaccine injections	21/2024	1.0	(0.6 ; 1.6)	24	1/2024	<0.1	(0 ; 0.3)	1
During 6-month follow-up period *	19/1925	1.0	(0.6 ; 1.5)	23	0/1925	0	(0 ; 0.2)	0
During the study	72/2024	3.6	(2.8 ; 4.5)	92	1/2024	<0.1	(0 ; 0.3)	1

	Nimenrix + routine paediatric vaccines (N=706)							
	All SAEs				Related SAEs			
Participants experiencing at least one SAE:	**n/M**	**%**	**(95% CI)**	**n SAEs**	**n/M**	**%**	**(95% CI)**	**n SAEs**
Within 7 days after any vaccine injections	2/706	0.3	(0 ; 1.0)	2	0/706	0	(0 ; 0.5)	0
Within 30 days after any vaccine injections	16/706	2.3	(1.3 ; 3.7)	16	0/706	0	(0 ; 0.5)	0
During 6-month follow-up period *	-	-	-	-	-	-	-	-
During the study	57/706	8.1	(6.2 ; 10.3)	69	0/706	0	(0 ; 0.5)	0

n: number of participants experiencing the endpoint listed in the first column; M: number of participants with available data for the relevant endpoint
n SAEs: number of SAEs
N: number of participants in safety analysis set post any dose
Percentages are based on M.
Related SAEs: relationship reported by an investigator as related to study vaccine: MenACYW/Menveo/ Nimenrix. If the relationship is missing, the SAE will be considered as related
Unsolicited systemic reactions related to MenACYW/Bexsero after booster vaccination for group 1 of MET52 are considered as related to MenACYW.
Contributing studies: MET33, MET41, MET42, MET52, MET58 and Group 1 and Group 2 of MET61
*Only MET41, MET42 and Group 1 and Group 2 of MET61 are considered
SafAS1 was defined as those participants who received at least 1 dose of the study vaccines and had any safety data available
Source: Modified from 5.3.5.3 Integrated Safety Summary Report Table 3.2.19

Four SAEs (3 SAEs experienced by participants who received MenACYW conjugate vaccine and 1 SAE experienced by a participant who received Menveo) were considered by the Investigator to be causally related to vaccination.

- One 2-month-old participant with a history of intractable fever experienced Grade 2 pyrexia which was reported by the Investigator as post-vaccination fever. The event started 8 hours following the 2-month vaccinations (first administration of Menveo administered concomitantly with Pentacel, Prevenar 13, RotaTeq, and ENGERIX-B), required hospitalisation and resolved 3 days later. The event was assessed as causally related to vaccination by the Investigator and Sponsor and did not lead to study discontinuation.
- A 3-month-old participant experienced petechial rash on both legs (Grade 1) 3 days after the first dose injection with MenACYW conjugate vaccine with the second dose of DTaP-HBV-IPV-Hib vaccine and rotavirus vaccine. The participant was admitted to the hospital for investigation on the same day. The treatment included paracetamol (Calpol). The next day, the participant was discharged from the hospital. Two weeks after the rash resolved, the participant received a second dose of control vaccine Bexsero concomitantly with a second dose of pneumococcal 13-valent conjugate vaccine and a third dose of DTaP-HBV-IPV-Hib vaccine. About 8 months later, the participant received the second dose of investigational MenACYW conjugate vaccine. The participant completed the study. The event of petechial rash on both legs was reported by the Investigator as related to the investigational vaccine administered concomitantly with DTaP-HBV-IPV-Hib vaccine and rotavirus vaccine; however, it was not possible to determine whether the cause was the investigational or non-investigational vaccines or another factor.
- One 12-month-old participant had an anaphylactic reaction 10 minutes after the MenACYW conjugate vaccine administration at 12 to 13 months of age visit. The event resolved but was life threatening and required hospitalisation. The event was assessed as causally related to vaccination by the Investigator and Sponsor and did not lead to study discontinuation.
- A 16-month-old participant experienced a Grade 3 febrile convulsion. The event started 13 days after the 15-month vaccinations (fourth dose of MenACYW conjugate vaccine administered concomitantly with Pentacel and Havrix), required healthcare contact and medication and resolved the same day. At the time of onset of this febrile convulsion, this participant had simultaneous AEs including a recurrent ear infection, infectious bronchiolitis, and a temperature of 102.5°F (39.2°C) and was being seen by the paediatrician (not Investigator) for these AEs. The febrile seizure had occurred at the paediatrician's office while receiving nebulizer treatment for wheezing. The event was assessed as causally related to vaccination by the Investigator but not causally related to the vaccination by the Sponsor. This event did not lead to study discontinuation.

Descriptive comparison of SAEs in infants 6 weeks to less than 12 months of age with toddler 12 months to 18 months of age

Overall, infants 6 weeks to less than 12 months of age experienced a higher rate of SAEs compared to toddlers 12 months to 18 months of age. The majority of SAEs were not considered related to vaccination. Related SAEs were rare (<0.1%). For both age groups, the rate of SAEs increased with time after vaccination (from 7 days to 30 days to the entire study duration). The highest rate of SAEs was observed in infants over the entire study duration (3.8%), but only <0.1% of these were considered related to vaccination.

Table 105: Overview of SAEs

	MenACYW + routine paediatric vaccines			
	6weeks to <12 months of age (SafAS2) (n=6060)		12-18 months of age (SafAS6) (n=5373)	
Participants experiencing at least one:	**All SAE**	**Related**	**All SAE**	**Related**
Within 7 days after any vaccination	0.4%	<0.1%	0.2%	<0.1%
Within 30 days after any vaccination	1.5%	<0.1%	0.5%	<0.1%
During 6-month follow-up period	0.4%	0%	1.1%	0%
During study	3.8%	<0.1%	1.3%	<0.1%

Source: Modified from 5.3.5.3 Integrated Safety Summary Report Table 4.1.2.19 and Table 5.2.19

Serious adverse events - Study MET39

During the study, 28 subjects reported at least one SAE at any time after vaccinations (2 [1.9%] in Group 1, 5 [4.9%] in Group 2, 7 [7.0%] in Group 3, 5 [6.8%] in Group 4, 1 [1.4%] in Group 5, 4 [7.7%] in Group 6, and 4 [8.2%] in Group 7). The SOC of Infections and Infestations was the most frequently reported across groups with 2 (1.9%) subjects in Group 1, 3 (2.9%) in Group 2, 5 (5.0%) in Group 3, 2 (2.7%) in Group 4, 3 (5.8%) in Group 6, and 1 (2.0%) in Group 7.

The number and percentage of subjects experiencing at least one SAE within 30 days after vaccinations were 2 (1.9%) in Group 1, 1 (1.0%) in Group 2, 1 (1.0%) in Group 3, 2 (2.7%) in Group 4, 1 (1.4%) in Group 5, 2 (3.8%) in Group 6, and 2 (4.1%) in Group 7.

There were 5 febrile convulsions reported after any vaccine injections during the study: 2 (2.0%) in Group 2 , 1 (1.0%) in Group 3 , and 1 (1.4%) in Group 5 , and 1 (2.0%) in Group 7 . Of these, no case occurred within 7 days after vaccination and only 1 case (1.4%) in Group 5 occurred within 30 days after the vaccine injections (9 days post vaccination) at 12 months. This subject had history of 3 days of fever and had the concomitant illness of herpangina; these events were considered unrelated to the study vaccines by the Investigator.

Deaths

There were 4 deaths reported among participants who received MenACYW conjugate vaccine during the study periods (3 participants from Study MET41 and 1 participant from Study MET42). All 4 events were considered unrelated to vaccination by the Investigator and the Sponsor. No deaths were reported among participants from studies MET33, MET52, MET58 and MET61.

- A 12-week-old participant from Study MET41 died due to non-accidental injury of the head (baby was shaken by his father, PT: head injury) 30 days after the first dose of MenACYW conjugate vaccine with routine paediatric vaccines. No autopsy or verbal autopsy was performed.
- A 12-week-old participant from Study MET41 had sudden unexplained death in infancy (PT, sudden infant death syndrome) 24 days after the first dose of MenACYW conjugate vaccine with routine paediatric vaccines. The narrative of the case states a pulmonary oedema as secondary cause of death as secondary cause of death, while the infant was sleeping between the parents. An autopsy was performed; however, no information whether a verbal autopsy was performed.
- A 6-month-old participant from Study MET41 was found by the parent to be unresponsive in bed (PT, unresponsive to stimuli) 4 days after the third dose of MenACYW conjugate vaccine with routine paediatric vaccines. An autopsy was performed; however, it was not reported if

verbal autopsy was performed. The infant had a medical history of neonatal hypoglycaemia and the narrative states that the case was considered as not related "based on autopsy result.

- A 2-month-old participant from Study MET42 died due to a cardiac arrest 6 days after receiving the first dose of MenACYW conjugate vaccine with routine paediatric vaccines at 2 months of age. Based on the provided narrative, the cardiac arrest case "was referred to the coroner of non-accidental trauma". The infant had retinal haemorrhages, severe candida rash and bruises at the shoulders but it was unknown whether an autopsy was performed; however, verbal autopsy was not performed.

Study MET39

Death occurred for 2 subjects in Group 4 (2.7% of the subjects in that group). These deaths (due to hypoxic ischemic encephalopathy and non-accidental head trauma) were considered not related to the study vaccine according to the Investigator and the Sponsor.

AESIs

The following AEs were captured as AESIs throughout the study periods:

- Generalized seizures (febrile and non-febrile)
- Kawasaki disease
- Guillain-Barré syndrome
- Idiopathic thrombocytopenic purpura (ITP)

All AESIs were generalized seizures, febrile and non-febrile except for one event of immune thrombocytopenia reported after the 6 months follow-up period.

After any dose administered 6 weeks to 18 months of age – SafAS1

A total of 36 participants (0.6%) who received MenACYW conjugate vaccine, 9 participants (0.4%) who received Menveo, and 3 participants (0.4%) who received Nimenrix experienced at least 1 AESI during the entire study period.

Within 7 days after any vaccination: A total of 3 AESIs were experienced by 3 participants (<0.1%) who received MenACYW conjugate vaccine. Two participants experienced febrile convulsions and 1 participant experienced seizure. None of the participants experienced any AESIs within 7 days after vaccination with Menveo or Nimenrix.

Within 30 days after any vaccination: A total of 11 AESIs were experienced by 10 participants (0.2%) who received MenACYW conjugate vaccine. The most frequently reported AESI was febrile convulsions experienced by 0.1% of participants who received MenACYW conjugate vaccine. None of the participants experienced any AESIs within 30 days of vaccination with Menveo and Nimenrix.

The majority of febrile seizure cases reported were assessed as unrelated to MenACYW conjugate vaccine, except one case on the 13th day after vaccination assessed as related to vaccination by the Investigator and as unrelated to vaccination by the Sponsor (see above SAEs).

During the entire study period: A total of 43 AESIs were reported by 36 participants (0.6%) who received MenACYW conjugate vaccine, 11 AESIs were reported by 9 participants (0.4%) who received Menveo, and 3 AESIs were reported by 3 participants (0.4%) who received Nimenrix. The most frequently reported AESI was febrile convulsions experienced by 0.4% of participants who received MenACYW conjugate vaccine, 0.3% of participants who received Menveo, and 0.3% of participants who received Nimenrix.

Table 106: All and related AESIs during the whole study – SafAS1

	MenACYW + routine pediatric vaccines (N=6060)								Menveo + routine pediatric vaccines (N=2024)							
	All AESIs				Related AESIs				All AESIs				Related AESIs			
Subjects experiencing at least one AESIs:	n	%	(95% CI)	n AESIs	n	%	(95% CI)	n AESIs	n	%	(95% CI)	n AESIs	n	%	(95% CI)	n AESIs
AESI	36	0.6	(0.4 ; 0.8)	43	1	<0.1	(0 ; 0.1)	1	9	0.4	(0.2 ; 0.8)	11	0	0	(0 ; 0.2)	0
Nervous system disorders	35	0.6	(0.4 ; 0.8)	42	1	<0.1	(0 ; 0.1)	1	9	0.4	(0.2 ; 0.8)	11	0	0	(0 ; 0.2)	0
Febrile convulsion	24	0.4	(0.3 ; 0.6)	28	1	<0.1	(0 ; 0.1)	1	7	0.3	(0.1 ; 0.7)	8	0	0	(0 ; 0.2)	0
Seizure	7	0.1	(0 ; 0.2)	8	0	0	(0 ; 0.1)	0	2	<0.1	(0 ; 0.4)	2	0	0	(0 ; 0.2)	0
Epilepsy	2	<0.1	(0 ; 0.1)	2	0	0	(0 ; 0.1)	0	1	<0.1	(0 ; 0.3)	1	0	0	(0 ; 0.2)	0
Seizure like phenomena	2	<0.1	(0 ; 0.1)	2	0	0	(0 ; 0.1)	0	0	0	(0 ; 0.2)	0	0	0	(0 ; 0.2)	0
Atonic seizures	1	<0.1	(0 ; 0.1)	1	0	0	(0 ; 0.1)	0	0	0	(0 ; 0.2)	0	0	0	(0 ; 0.2)	0
Infantile spasms	1	<0.1	(0 ; 0.1)	1	0	0	(0 ; 0.1)	0	0	0	(0 ; 0.2)	0	0	0	(0 ; 0.2)	0
Petit mal epilepsy	0	0	(0 ; 0.1)	0	0	0	(0 ; 0.1)	0	0	0	(0 ; 0.2)	0	0	0	(0 ; 0.2)	0
Blood and lymphatic system disorders	1	<0.1	(0 ; 0.1)	1	0	0	(0 ; 0.1)	0	0	0	(0 ; 0.2)	0	0	0	(0 ; 0.2)	0
Immune thrombocytopenia	1	<0.1	(0 ; 0.1)	1	0	0	(0 ; 0.1)	0	0	0	(0 ; 0.2)	0	0	0	(0 ; 0.2)	0

	Nimenrix + routine pediatric vaccines (N=706)							
	All AESIs				Related AESIs			
Subjects experiencing at least one AESIs:	n	%	(95% CI)	n AESIs	n	%	(95% CI)	n AESIs
AESI	3	0.4	(0.1 ; 1.2)	3	0	0	(0 ; 0.5)	0
Nervous system disorders	3	0.4	(0.1 ; 1.2)	3	0	0	(0 ; 0.5)	0
Febrile convulsion	2	0.3	(0 ; 1.0)	2	0	0	(0 ; 0.5)	0
Seizure	0	0	(0 ; 0.5)	0	0	0	(0 ; 0.5)	0
Epilepsy	0	0	(0 ; 0.5)	0	0	0	(0 ; 0.5)	0
Seizure like phenomena	0	0	(0 ; 0.5)	0	0	0	(0 ; 0.5)	0
Atonic seizures	0	0	(0 ; 0.5)	0	0	0	(0 ; 0.5)	0
Infantile spasms	0	0	(0 ; 0.5)	0	0	0	(0 ; 0.5)	0
Petit mal epilepsy	1	0.1	(0 ; 0.8)	1	0	0	(0 ; 0.5)	0
Blood and lymphatic system disorders	0	0	(0 ; 0.5)	0	0	0	(0 ; 0.5)	0
Immune thrombocytopenia	0	0	(0 ; 0.5)	0	0	0	(0 ; 0.5)	0

n: number of subjects experiencing the endpoint listed in the first column
n AESIs: number of AESIs
N: number of subjects in safety analysis set post any dose
Percentages are based on N.
Related AESIs: relationship reported by an investigator as related to study vaccine: MenACYW/Menveo/Nimenrix. If the relationship is missing, the AESI will be considered as related
Unsolicited systemic reactions related to MenACYW/Bexsero after booster vaccination for group 1 of MET52 are considered as related to MenACYW.
Contributing studies: MET33, MET41, MET42, MET52, MET58 and Group 1 and Group 2 of MET61
Study: OVERALL Program: t03xto5x020to23n33to36.sas Datasets=ADSL ADAE Output: PRODOPS/SP0047/OVERALL/ISS_2024/REPORT/OUTPUT/T032036_x.pdf (10SEP2024 8:54)

No cases of GBS and Kawasaki disease were reported in the integrated safety analysis. There were two cases of thrombocytopenia reported (one case of immune thrombocytopenia, an AESI, and one case of thrombocytopenia, not an AESI). Both were assessed as unrelated to vaccination.

Of note, **in Study MET39**, there were 2 cases of Kawasaki disease after any vaccine injections during the study: 1 (1.0%) in Group 2 and 1 (1.0%) in Group 3. Both cases occurred more than 30 days after vaccination and involved co-administration of multiple concomitant licensed vaccines, including rotavirus vaccine. One report had an alternative infectious aetiology and risk factors. These events were considered unrelated to the study vaccines.

Comparison of infants 6 weeks to less than 12 months of age vs toddler 12 months to 18 months of age

The majority of AESIs were not considered related to vaccination. Related AESIs (febrile seizures) occurred in one toddler aged 12 months to 18 months (<0.1%).

Table 107: Overview of AESIs

	MenACYW + routine pediatric vaccines

	6 weeks to <12 months of age (SafAS2) (n=6060)		12-18 months of age (SafAS6) (n=5373)	
Participants experiencing at least one:	**All AESI**	**Related**	**All AESI**	**Related**
Within 7 days after any vaccination	<0.1%	0%	<0.1%	0%
Within 30 days after any vaccination	<0.1%	0%	0.1%	<0.1%
During 6-month follow-up period*	<0.1%	0%	0.3%	0%
During study	0.4%	0%	0.3%	<0.1%

*Only applicable for studies MET41, MET42, and MET61
Source: Modified from 5.3.5.3 Integrated Safety Summary Report Table 4.1.2.32 and Table 5.2.32

Safety in special populations

Subgroup Analysis by Gestational Age At Birth

A total of 237 participants (pre-term at birth, range: 31 weeks to 36 weeks) and 4483 participants (full-term at birth) are among those who received MenACYW conjugate vaccine.

No participant born pre-term experienced an immediate unsolicited AE or an immediate unsolicited AR. Among participants who received MenACYW conjugate vaccine, 10 participants born full-term (0.2%) and 4 participants born full-term (<0.1%) experienced an immediate unsolicited AE and an immediate unsolicited AR, respectively.

The percentage of participants who experienced at least 1 solicited injection site reaction after any vaccine injection was 75.9% among participants born pre-term and 83.4% among participants born full-term. The percentage of participants who experienced at least 1 solicited systemic reaction after any vaccine injection (meningococcal vaccines and routine pediatric vaccines) was 78.9% among participants born pre-term and 86.0% among participants born full-term.

The percentage of participants who experienced at least 1 unsolicited non-serious AE after any vaccine injection was 54.4% among participants born pre-term and 60.8% among participants born full-term. The percentage of participants who experienced at least 1 unsolicited non-serious AR after any vaccine injection was 4.6% among participants born pre-term and 10.1% among participants born full-term.

No participant born pre-term experienced an AE leading to study discontinuation; there were 8 participants born full-term (0.2%) who were withdrawn from the study due to AEs within 30 days of any vaccine injection.

During the entire study period, a total of 14 participants born pre-term (5.9%) and 249 participants born full-term (5.6%) experienced at least 1 SAE. A total of 1 participant born pre-term (0.4%) and 32 participants born full-term (0.7%) experienced at least 1 AESI.

Four deaths were reported among the participants born full-term who received MenACYW conjugate vaccine. None of the deaths reported were assessed as causally related to vaccination.

Subgroup Analysis by Gender

The safety results were comparable between female and male participants.

Subgroup Analysis by Race

The safety results across race were comparable.

Safety related to drug-drug interactions and other interactions

In Studies MET33, MET41, MET42, MET52, MET58, and MET61, MenACYW conjugate vaccine was given concomitantly with routine paediatric vaccines according to schedules provided by local guidelines for paediatric immunisation.

In Study MET33, conducted in Mexico and the Russian Federation, MenACYW conjugate vaccine was given concomitantly with Prevenar 13, Hexacima, VARIVAX, M-M-RII to infants in Mexico; in the Russian Federation, MenACYW conjugate vaccine was given concomitantly with Prevenar 13, Pentaxim, ENGERIX-B, and MMR vaccines.

In Studies MET41 and MET42, conducted in the US, MenACYW conjugate vaccine or Menveo was given concomitantly with routine paediatric vaccines, including DTaP-IPV/Hib, PCV13, rotavirus, HepB, MMR, Varicella, and HepA.

In Study MET52, conducted in the UK, MenACYW conjugate vaccine and/or Meningococcal Group B (Bexsero) was given concomitantly with Infanrix hexa (Combined Diphtheria-Tetanus acellular Pertussis [DTPa], Hepatitis B, Inactivated Poliovirus, and Haemophilus influenzae type b Vaccine; DTPa-HBVIPV+ Hib), Rotarix (rotavirus vaccine; RV), Prevenar 13.

Table 108: Study MET52 safety overview after vaccine injection at 12 through 13 months of age - Safety analysis set 4

	Group 1 (N=303)			Group 2 (N=306)			Group 3 (N=151)		
Subjects experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Within 30 mins after any vaccine injections									
Immediate unsolicited AE	0/303	0	(0 ; 1.2)	1/306	0.3	(0 ; 1.8)	0/151	0	(0 ; 2.4)
Immediate unsolicited AR	0/303	0	(0 ; 1.2)	1/306	0.3	(0 ; 1.8)	0/151	0	(0 ; 2.4)
Solicited reaction within solicited period after any vaccine injections	295/298	99.0	(97.1 ; 99.8)	256/302	84.8	(80.2 ; 88.6)	144/149	96.6	(92.3 ; 98.9)
Solicited injection site reaction	275/298	92.3	(88.6 ; 95.0)	217/302	71.9	(66.4 ; 76.9)	137/149	91.9	(86.4 ; 95.8)
MenACYW	242/298	81.2	(76.3 ; 85.5)	217/302	71.9	(66.4 ; 76.9)	-	-	-
Bexsero	265/297	89.2	(85.1 ; 92.5)	-	-	-	137/149	91.9	(86.4 ; 95.8)
Solicited systemic reaction	267/298	89.6	(85.6 ; 92.8)	198/302	65.6	(59.9 ; 70.9)	127/149	85.2	(78.5 ; 90.5)
Within 30 days after any vaccine injections									
Unsolicited AE	171/303	56.4	(50.6 ; 62.1)	164/306	53.6	(47.8 ; 59.3)	71/151	47.0	(38.9 ; 55.3)
Unsolicited AR	65/303	21.5	(17.0 ; 26.5)	28/306	9.2	(6.2 ; 13.0)	19/151	12.6	(7.7 ; 19.0)
Unsolicited non-serious AE	170/303	56.1	(50.3 ; 61.8)	163/306	53.3	(47.5 ; 59.0)	71/151	47.0	(38.9 ; 55.3)
Unsolicited non-serious AR	64/303	21.1	(16.7 ; 26.2)	27/306	8.8	(5.9 ; 12.6)	19/151	12.6	(7.7 ; 19.0)
Unsolicited non-serious injection site AR	56/303	18.5	(14.3 ; 23.3)	22/306	7.2	(4.6 ; 10.7)	18/151	11.9	(7.2 ; 18.2)
Unsolicited non-serious systemic AE	146/303	48.2	(42.4 ; 54.0)	158/306	51.6	(45.9 ; 57.4)	67/151	44.4	(36.3 ; 52.7)
Unsolicited non-serious systemic AR	8/303	2.6	(1.1 ; 5.1)	5/306	1.6	(0.5 ; 3.8)	1/151	0.7	(0 ; 3.6)
Unsolicited non-serious systemic AR related to NIMP	0/303	0	(0 ; 1.2)	0/306	0	(0 ; 1.2)	0/151	0	(0 ; 2.4)
AE leading to study discontinuation	0/303	0	(0 ; 1.2)	0/306	0	(0 ; 1.2)	0/151	0	(0 ; 2.4)
SAE	2/303	0.7	(0.1 ; 2.4)	8/306	2.6	(1.1 ; 5.1)	0/151	0	(0 ; 2.4)
Death	0/303	0	(0 ; 1.2)	0/306	0	(0 ; 1.2)	0/151	0	(0 ; 2.4)
AESI	0/303	0	(0 ; 1.2)	1/306	0.3	(0 ; 1.8)	0/151	0	(0 ; 2.4)
During the study									
SAE	2/303	0.7	(0.1 ; 2.4)	10/306	3.3	(1.6 ; 5.9)	0/151	0	(0 ; 2.4)
Death	0/303	0	(0 ; 1.2)	0/306	0	(0 ; 1.2)	0/151	0	(0 ; 2.4)
AESI	0/303	0	(0 ; 1.2)	1/306	0.3	(0 ; 1.8)	0/151	0	(0 ; 2.4)

n: number of subjects experiencing the endpoint listed in the first column; M: number of subjects with available data for the relevant endpoint
N: number of subjects in safety analysis set for vaccination at 12 through 13 months of age
Percentages are based on M.
AR: Reactions related to IMP (MenACYW/Bexsero); Unsolicited injection site reactions related to NIMP (concomitant routine vaccines) are reported separately
Subjects are summarized according to vaccines received at 12 through 13 months of age.
Subjects received MenACYW and Bexsero are summarized under "Group 1"; subjects received MenACYW only are summarized under "Group 2";
subjects received Bexsero only are summarized under "Group 3".
Study: MET52 Program: t08023to27.sas Datasets=ADSL ADAE ADRC Output: PRODOPS/SP0047/MET52/CSR_01/REPORT/OUTPUT/T08027_x.pdf (15JUN2023 7:38)

In Study MET58, conducted in Europe (Czech Republic, Romania, Sweden, Finland, Italy, Poland, and Spain), MenACYW conjugate vaccine or Nimenrix was given concomitantly with routine paediatric vaccines DTaP-IPV-HB-Hib, Prevenar 13 (in Italy and Spain only), Synflorix, M- M-RVAXPRO.

In Study MET61, conducted in the US and Puerto Rico, MenACYW conjugate vaccine and Menveo were administered concomitantly with DTaP-IPV/Hib or DTaP-IPV-HepB combination vaccine, PCV13, rotavirus, HepB, Hib, MMR, and varicella vaccines.

Discontinuation due to adverse events

Eight participants (0.1%) who received MenACYW conjugate vaccine concomitantly with routine paediatric vaccines and 3 participants (0.1%) who received Menveo concomitantly with routine paediatric vaccines experienced at least 1 AE that led to study discontinuation. None of the participants who received Nimenrix concomitantly with routine paediatric vaccines experienced any AEs that led to study discontinuation. Three AEs in 2 participants that led to study discontinuation were considered as related to study vaccines (MenACYW conjugate vaccine coadministered with routine paediatric vaccines)

None of the participants who received a booster dose of MenACYW conjugate vaccine, Menveo or Nimenrix experienced any AEs that led to study discontinuation.

Post marketing experience

Since the first marketing authorisation in April 2020 in the US, eight 6-month Periodic benefit-risk evaluation reports (PBRERs) and five 1-year PBRERs have been released that globally covered the period from 20 April 2020 to 19 April 2025. Post-marketing safety data in the population from 12 to 23 months of age from countries where the MenACYW conjugate vaccine is authorised from 12 months of age and older (single dose schedule) is part of the PBRERs.

MenACYW conjugate vaccine is not indicated in individuals younger than 12 months of age, except in the Russian Federation and US, where it was recently approved (20 May 2025 and 23 May 2025, respectively).

2.5.1. Discussion on clinical safety

Methods

Six phase III studies (MET33, MET41, MET42, MET52, MET58, MET61) were considered for the integrated summary of safety analysis. The safety evaluation methods and population (children between 6 weeks and 3 months of age at first vaccination, except for Study MET61: 6 months of age) are overall considered sufficiently similar for a pooled integrated analysis.

The safety analysis strategy is generally endorsed. Safety data were evaluated descriptively, which is acceptable. Safety data collection methods are deemed appropriate for the evaluated population.

Most studies employed Menveo as meningococcal vaccine comparator, which is approved in the US but not in the EU for children below 2 years of age. However, this is seen less critical for the safety evaluation regarding the nature and frequency of AE. Nimenrix was only used as comparator in Study MET58 (~ 900 receiving at least one MenACYW dose, and 706 receiving Nimenrix). Thus, the Nimenrix comparator group is of limited size. The safety follow-up for SAEs and AESIs was 6-month after the last vaccination in study MET41, MET42 and MET61 and 30 days in study MET52, MET33 and MET58, which is considered rather short. However, no safety concern in the dataset with longer follow-up arises. Although a 6-month follow-up is preferrable, no concern is raised in this regard, additionally considering that more than half of the safety database was enrolled in studies with a longer follow-up.

The integrated studies evaluated different schedules for the primary vaccination of infants (1, 2 or 3 priming doses followed by a booster dose in the 2nd year of life [1+1, 2+1, 3+1]). The majority of the

safety database is informed by studies employing a 3+1 schedule, which is considered also relevant for the sought after 2+1 regimen.

In all studies, meningococcal vaccines administration was embedded in a vaccination scheme of other childhood vaccines, which is generally seen inevitable given the study population of infants. The employed childhood vaccines and schedules are largely considered relevant also for the EU although Pentacel is not approved in the EU. However, this issue is not pursued further as not seen critical for the safety evaluation and pertinent statements as regards DTaP-IPV/Hib were removed from the SmPC. There was largely no control group with only childhood vaccines (or MenACYW) for comparison.

In addition to above mentioned studies, study MET39 is noted, which evaluated the safety profile of MenACYW administered at 5 different schedules in infants from 2 month of age (1+1, 2+1, 3+1, 1 toddler dose and concomitantly with routine paediatric vaccinations; n overall = 550). The study was submitted as part of the initial MAA data package but the included patient population did not reflect the intended target population of the initial MAA. Therefore, no assessment of the immunogenicity or safety results was done. The study was largely not addressed by the MAH in the current submission. Overall, no specific safety concern arises from this single study but the occurrence of two cases of Kawasaki disease is noted (further discussed as AESIs below).

Exposure

The safety database comprises 6060 infants exposed to at least one dose of MenACYW and 4880 received at least 2 doses during infancy. In addition, 5373 toddlers were exposed to a booster dose after a primary infant series (1, 2 or 3 doses). The safety database is considered sufficiently large.

The demographic baseline characteristics of the pooled analysis population are deemed representative of the target population (healthy infants from 6 weeks of age). Overall, 144 infants with 6 weeks of age (42-48 days of age) were exposed to MenACYW and 623 infants received MenACYW between 42-59 days of age (roughly 6 weeks to 2 months of age). No safety subgroup analysis per age at first vaccination was provided for the integrated safety summary but no concern arose based on a respective subgroup analysis in Study MET58, although the small size of the <2 months of age subgroup in this study (112 MenACYW Group 1 and 113 Nimenrix Group 2, respectively) limits this analysis.

Adverse events

In the integrated analysis, the vast majority of participants experienced at least 1 solicited AR after any dose in all three meningococcal vaccine groups (MenACYW 88.9%, Menveo 85.6%, Nimenrix 96.5% [MenACYW Study MET58 Group 1: 97.3%]). Similarly, at least 1 solicited AR was reported by 86.8% and 74.5% participants following any dose of the primary infant series and the booster dose, respectively, in the MenACYW group. Across all studies, solicited injection site reactions and systemic reactions were the most commonly reported AEs. The safety profile appears largely consistent with the integrated safety population, despite differences in the reporting frequency of some PTs, and overall comparable across meningococcal vaccine groups, with some numerical differences noted. However, the solicited systemic reaction/AE/AR/SAE reporting rate was generally higher in the only Nimenrix-controlled trial MET58, conducted in EU countries, in comparison to the integrated safety summary (see *Table 92* and *Table 93*), which limits the comparative safety assessment based on the integrated analysis.

Immediate unsolicited reactions

Immediate unsolicited AEs occurred infrequently in the MenACYW group (0.1% [7/6060] after any infant dose and <0.1% [4/5373] in toddlers 12 to 18 moa after the booster dose). No trend for increasing rates of immediate unsolicited AEs with subsequent doses was apparent.

In total, 5 events in 5 participants were considered as related and included erythema (2 participants), rash macular, syncope and an anaphylactic reaction (following a booster dose). No new safety concern as regards immediate allergic reactions arises. Two cases of hypersensitivity or allergy/allergic events were considered related to administration of MenACYW by the Investigator. Events pertained to "conjunctivitis allergic" and "injection site hypersensitivity", the latter further described as plaster allergy. The MAH's argumentation that these two cases are not relevant for the frequency estimation of hypersensitivity ADRs (currently reflected as "unknown" in the SmPC) is accepted. It is agreed that there is likely an alternative aetiology, not warranting a revision of the current frequency classification of the broad hypersensitivity term in the SmPC. Three immediate events of flushing were reported in two participants. Flushing was included into the corresponding ADR table with frequency rare, which is endorsed.

Solicited reactions

Overall, no concerns are raised regarding the reported solicited events. Solicited reactions were mostly Grade 1 to Grade 2 events and the majority resolved within 1-3 days. No significant difference regarding the solicited event pattern after any dose and each dose of the infant primary series or toddler booster was apparent between MenACYW, Menveo and Nimenrix (in Study MET58).

In the integrated safety analysis **after any dose**, 72.5% of participants in the MenACYW reported at least one **solicited injection site** reaction (tenderness, erythema, swelling), and 83.3% in the MenACYW group at least one **solicited systemic reaction** (fever, vomiting, crying abnormal, drowsiness, appetite lost, irritability). Irritability (74.6%), crying abnormal (66.2%) and drowsiness (61.7%) were the most frequently reported solicited reactions following MenACYW. Fever occurred in 32.2% of participants exposed to MenACYW and the frequency of Grade 3 fever (>39.5 °C) was low (1.6%). Severe fever ≥40°C occurred in 0.6% after any dose (~0.4% after any infant or toddler dose). MenACYW appeared slightly more reactogenic compared to Menveo, as the majority of solicited events (all but injection site tenderness) occurred at a numerically higher frequency in the MenACYW intervention group (~2.5-6% points higher). A similar trend was notable after the booster dose for all categories (≤5% points higher incidence in the MenACYW group). However, this difference is considered not clinically relevant. The pattern of solicited reactions was comparable following any dose of the primary infant series and the booster dose. Notably, the frequency of **solicited reactions (local and systemic)** was higher after **any MenACYW infant dose** in comparison to **the toddler booster dose** (injection site: 64.3% vs 50.8%, systemic: 80.2% vs 63.8%). A similar trend was seen for Grade 3 reactions (injection site: 5.4% vs 2.9%, systemic: 13.0% vs 6.1% booster toddler), which however did not concern fever. This was also apparent in both comparator groups although only for some events and less pronounced in the Nimenrix group. The incidence of solicited reactions was largely comparable across subsequent infant doses and the booster dose, with mostly a decreasing trend after dose 1 for solicited systemic reactions (any solicited systemic reaction dose 1: 71.1%, dose 2: 67.2%, dose 3: 62.0%, booster: 63.8%). However, a trend towards higher proportions of subjects reporting fever at subsequent vaccinations following the first administration was observed (9.1%, 18.3%, 15.7%, 16.0% for first, second, third (mainly US studies MET41, MET42), and booster injection; in comparison: 24.8% after any infant dose). Similarly, the proportion of subjects with Grade 2 fever (>38.5°C to ≤39.5°C) increased following the first dose (1.8%, 5.5%, 4.8%, and 4.7).

Unsolicited adverse events and adverse reactions

Unsolicited AEs occurred in 59.5% participants following **any vaccine injection** in the MenACYW group. The nature and frequency were overall comparable to the Menveo group (54.1%) and to the Nimenrix group (68.0%, Study MET58 MenACYW Group 1: 65.8%). Reported AEs are generally in line with common conditions in the evaluated age group.

Related AEs (ARs) after any dose, not captured as solicited events, were reported slightly more often in the MenACYW group (9.3%) in comparison to the Menveo group (6.9%) and were comparable to Nimenrix in Study MET58 (MenACYW Group1 18.4% vs Nimenrix 18.1%). The majority of unsolicited ARs lasted 1-7 days and were mainly Grade 1 to Grade 2. Related events after any MenACYW dose were mostly linked to injection site reactions such as bruising (6.1%) and diarrhoea was the most frequently reported non-serious systemic ARs (0.6%). This was apparent after the primary infant series and the toddler booster dose, along with rash following the booster dose (0.2%). Overall, 6.0% of participants following any dose of the primary infant series and 4.9% after the booster dose reported unsolicited ARs.

No concerning difference in unsolicited ARs frequency is noted.

Generally, the nature of vaccine-related AEs does not raise any concern. The majority of vaccine-related AEs concern solicited injection site reactions and solicited systemic reactions, discussed above. The provided justification regarding the ADR table (individuals 6 weeks through 23 months of age) in section 4.8 of the SmPC is acceptable. Of note, upon re-evaluation by the MAH, exclusion of nasopharyngitis and URTI, which were initially included in the ADR table based on relatedness assessment by the Investigator, was proposed. This is acceptable as alternative explanations such as region-specific reporting practises and the temporal association of reported events appear reasonable.

The safety profile of the toddler booster dose appears largely consistent with a primary dose in the second year of life.

Serious adverse events and deaths

During the entire study duration and after any vaccine dose, 4.8% of participants in the MenACYW integrated group reported 386 SAEs, which was largely similar to the Menveo group (3.6%) and the Nimenrix group in Study MET58 (7.3% MenACYW vs 8.1% Nimenrix). The vast majority was reported as recovered or resolved (362 out of 386 SAEs [94%] in the MenACYW group). A low number of SAEs were considered related and were reported for 3 participants enrolled in the MenACYW group and 1 participant from the Menveo group, which all resolved. SAEs considered related in the MenACYW group included petechial rash (3 days after the first dose, Grade 1), anaphylactic reaction (immediate reaction, see above) and febrile convulsion. Regarding the latter event, 0.2% (15/6060) in the MenACYW group reported SAEs in the SOC nervous system disorder within 30 days of vaccination (5/6060 participants within 7 days; none in the comparator groups) and 0.7% (MenACYW) vs 0.4% (Menveo) vs 0.6% (Nimenrix) during the entire study. These mainly concerned febrile convulsion/seizures, further discussed as AESIs below.

Most common SAEs reported during the entire study concerned infections and febrile convulsions/seizures. It was noted in previous P46 procedures (Study MET41 EMEA/H/C/005084/P46/007.1, Study MET33 EMEA/H/C/005084/P46/009) that SAEs of lower respiratory tract infections (LRTIs)/gastrointestinal infections and seizures/convulsions should be discussed in detail once all data of the clinical program in subjects <12 years become available. Serious infections were slightly more frequently reported following any infant MenACYW dose compared to toddlers receiving the booster dose (within 7-days: 0.2% vs 0.1%, within 30-days: 0.9% vs 0.3%, entire study: 2.2% vs 0.7%), which mostly concerned LRTIs. It can be generally agreed that this observation per age group likely reflects the epidemiology of serious LRTIs. However, a numerical higher proportion of participants reported **SAEs for infections and infestations** within 7 and 30 days **after any vaccine administration** in the MenACYW group (0.3% 21/6060 and 1.2% 73/6060, respectively) in comparison to the other two comparator groups in the integrated safety summary (Menveo 0.1% 3/2024 and 0.6% 13/2024, respectively) and in Study MET58 (0.7% 5/696 and 1.9% 13/696 MenACYW [plus 2/112 Group 3 and 1/108 Group 4] vs 0 and 0.8% 6/706 Nimenrix,

respectively). During the entire study, SAE reporting rate for the SOC infections and infestation was comparable across intervention groups (also in Study MET58). The MAH provided a comprehensive discussion regarding serious infections, with particular focus on serious respiratory infections in individuals <2 yoa. Although there were numerical differences between meningococcal vaccination group, no concerning pattern of reported infections or time to onset was apparent after MenACYW administration. Observed numerical differences may be a chance finding. This conclusion was supported by review of the MAH's pharmacovigilance database. Observations were consistent with common early childhood infections and their epidemiology. It is agreed that the provided cumulative evidence does not conclusively support a causal association between serious infections, particularly respiratory tract infections, and MenACYW administration. No new safety concern arises based on current evidence related to serious infections. Injection site infections reported post-marketing are further commented below.

The number of **deaths** in the 6 studies from the integrated analysis was low. In total, 4 out of 6060 participants died in the MenACYW group and none in the other comparator groups. These deaths occurred in Study MET41 and Study MET42. One death happened due to a head-injury caused by parental shaking, and one due to cardiac arrest as primary cause of death 6 days after the first MenACYW dose. Based on the provided narrative, the cardiac arrest case "was referred to the coroner of non-accidental trauma". The infant had retinal haemorrhages, severe candida rash and bruises at the shoulders but it is unknown whether an autopsy was performed. No primary cause of death was reported for 2 out of the 4 cases (PT sudden infant death syndrome in a 12 week old infant and PT unresponsive to stimuli in a 6 month old participant). Both occurred in Study MET41 and no other concerning unsolicited AEs were noted in the respective listing. The narrative of the sudden infant death case (24 days after the first vaccination) states a pulmonary oedema as secondary cause of death, while the infant was sleeping between the parents. For the unresponsive to stimuli case (4 days following the 3rd vaccination), the infant had a medical history of neonatal hypoglycaemia and the narrative states that the case was considered as not related "based on autopsy result". The cause and manner of death was considered undetermined by the pathologist. There was no evidence of an acute inflammatory state and causality assessment by the Investigator remained not related based on autopsy results. The MAH contextualised the number of deaths and the occurrence of sudden infant death syndrome in the US studies MET41 and MET42, which are comparable to the (post neonatal) infant mortality rate and the background incidence of sudden infant death syndrome. In addition, the MAH informed that there were no cases of sudden infant death syndrome reported during post-marketing surveillance, which is reassuring.

Adverse events of special interest

AESIs were reported at low rate in the MenACYW group (43 AESIs in 36/6060 participants, 0.6%) during the entire study, which was overall comparable to the other meningococcal vaccine groups (Menveo: 0.4%; Nimenrix: 0.4% [Study MET58 MenACYW: 0.4%]). All but two events, 1 each in the MenACYW and Menveo group were recovered/recovering (1 with sequelae). AESIs concerned generalised seizures except for one case of immune thrombocytopenia. Within 30-days after any vaccination, the AESI frequency was highest in the MenACYW group (10 participants, 0.2%; Menveo and Nimenrix: 0%). One febrile convulsion reported 13-days after the booster dose (4th dose) in a 16-months old participant was considered related to MenACYW by the Investigator but not the Sponsor due to another possible aetiology (acute concomitant infection) and a medical history of febrile convulsions. This can be followed. Three AESIs including 2 events of febrile convulsion and 1 event of seizure were reported within 7 days after any vaccine in the MenACYW arm and all were considered unrelated, which is agreed. The risk of convulsions was systematically assessed previously within the scope of a type II variation (EMEA/H/C/005084/II/0037, approved on 23 January 2025), leading to the inclusion of febrile convulsion and seizures in section 4.8 of the SmPC with frequency "unknown",

which is still deemed acceptable as no new evidence arose in this submission. Although in the integrated analysis, febrile convulsions/seizures had a higher reporting rate within 30-days after vaccination in the MenACYW group compared to Menveo and Nimenrix, current data do not conclusively point towards a higher risk with MenACYW vaccination in comparison to Nimenrix or Menveo. The unknown frequency of febrile convulsions and seizures remains an uncertainty.

Regarding the immune thrombocytopenia that occurred in Study MET58, the non-relatedness assessment is agreed based on the provided narrative.

Two cases of Kawasaki disease occurred in Study MET39, one 106 days following the 3rd vaccination, where the participant reported fever and rash one week prior the diagnosis of Kawasaki disease, and one case 52 days following the second vaccination. The latter participant was additionally diagnosed with pneumonia 2 days prior the event of Kawasaki disease was noted. The cases were judged as not related to vaccination which is agreed.

Safety in special populations

In trials MET41, MET42, and MET58, 237 preterm infants of gestational age ranging from 31-36 weeks were included in total, 15 of which were included in the pivotal trial MET58. As discussed above and similar to the overall population, the majority of the safety database for pre-term infants is informed by studies using a 3+1 dosing scheme, compared to the 2+1 dosing scheme in the EU-based study. However, safety data from a 3+1 schedule is also considered relevant for a 2+1 regimen. Within the combined safety pool, the reactogenicity was comparable between pre-term infants and full-term infants with a numerical trend towards lower reactogenicity for preterm infants, and a slightly numerically higher proportion of preterm infants experiencing grade 3 solicited reactions. Considering that safety data for infants with a history of preterm birth is limited and that no data on very premature infants with a gestational age of ≤28 weeks are available, a general warning as regards the potential risk of apnoea upon administering the primary immunisation series to very premature infants was included in section 4.4 of the SmPC, as already included in other authorised vaccines to be used in this age group.

Regarding the sub-group analysis of subjects related to gender and race, no trends towards differences in the safety profile of MenACYW were observed for male or female subjects. In addition, the safety results were comparable between the racial sub-populations.

Concomitant administrations

Since no control group with only childhood vaccines was largely included, no conclusions can be drawn regarding potential differences between concomitant and separate vaccinations, especially applicable for systemic events. However, no clinically significant difference in the safety profile between MenACYW, Menveo and Nimenrix was apparent. Summarised data for solicited injection site reaction per vaccines was provided.

No apparent trend as regards local reactogenicity after any dose of MenACYW concomitantly administered with other childhood vaccines was identified, while employed childhood vaccines differed across studies.

Study MET52 evaluated co-administration with Bexsero in individuals at 12-month of age that previously received either one dose of MenACYW at 3 months of age or Bexsero at 2 and 4 months of age, embedded within other routine childhood vaccines. Safety data from this study were discussed in a previous type II variation (EMEA/H/C/005084/II/0027, opinion on 11/04/2024). Overall and as previously noted in the respective type II assessment report, no unexpected safety finding was apparent upon co-administration of MenACYW and Bexsero in toddlers. However, a higher proportion of subjects with unsolicited ARs (group 1 [Bexsero+MenACYW]: 21.5%, group 2 [MenACYW]: 9.2%

and group 3 [Bexsero]: 12.6%) and grade 3 solicited injection site reactions (MenACYW injection site group 1: 9.4%, group 2: 3.6%; Bexsero injection site group 1: 26.9%, group 3: 20.8%) was observable in the co-administration intervention group. This is reflected in section 4.8 of the SmPC.

The use of prophylactic medication appears overall balanced across study groups in the individual studies (~4-15%, ~56-64% in study MET52). Use of prophylactic antipyretics and analgesics was highest in the MenACYW group (12.2%), followed by the Menveo (7.8%) and the Nimenrix (2.4%) groups after any dose (SafAS1). This trend was mainly driven by study MET52, in which only MenACYW was co-administered with Bexsero. It appears therefore plausible that the observed higher prophylactic antipyretic use in the pooled MenACYW group reflects a pooling artefact rather than a true difference between groups.

Discontinuations

Across the 6 integrated studies, 11 participants reported an AE leading to discontinuation within 30 days after any vaccination, reflecting a low discontinuation rate (MenACYW n=8, 0.1% and Menveo n= 3, 0.1%). No AEs in Study MET58 (including the Nimenrix group) led to discontinuation within 30 days following vaccination. Two participants in the MenACYW group experienced related AEs pertaining to injection site (tenderness, erythema, rash) and systemic reactions (fever, irritability and crying). The remaining AEs were considered not related and no accumulative pattern as regards a certain AE is evident.

Post marketing experience

The MAH provided a comprehensive evaluation concerning serious and non-serious (respiratory) infections, also considering post-marketing data (unsolicited reports; see above, discussion on serious adverse events).

Several cases from post-marketing reporting (unsolicited cases) regarding injection/vaccination site infections were noted and the MAH provided a comprehensive evaluation report on the occurrence of injection site infections. Few cases were reported in pooled datasets from clinical trials that were considered as related by the Investigator (2 cases of injection site cellulitis of which one started on the same day as vaccination and 1 was not associated with the MenQuadfi administration site according to the MAH; 1 case of injection site infection with further details regarding the infection missing; all in individuals ≥12 months of age). Further, there were 27 relevant cases retrieved from the MAH's pharmacovigilance database, of which 6 represent SAEs from clinical trials. However, those did not occur at the MenQuadfi administration site and the time to onset is rather long with respect to MenQuadfi administration (time to onset ≥79 days, except for 1 case 16 days). The remaining 21 cases originated from unsolicited reporting (10 serious, 11 non-serious), including 17 cases for MenQuadfi and 4 cases involving meningococcal vaccines of unknown manufacturer.

Most retrieved unsolicited cases pertained to cellulitis (n=17), of which 8 were serious. The Brighton Collaboration Case Definition (BCCD) criteria for cellulitis and abscess were applied to assign diagnostic certainty, which is in principle endorsed. However, cases from spontaneous reporting can fall into lower levels of diagnostic certainty as they may not contain the level of required detail. This is a limitation and may result in case assignment of lower diagnostic certainty. Challenges related to the case classification for cellulitis at the vaccination site and their distinction from more severe non-infectious injection site reactions are acknowledged. The required detail to definitely determine whether the events have been caused by local reactions or infection is not always available in respective reports. Among 17 cellulitis cases, 7 presented with comparably higher diagnostic certainty according to BCCD criteria; of which 4 are linked with additional uncertainties. Likewise, but irrespective of BCCD criteria, 8 out of 17 cellulitis cases could be noted that received only MenQuadfi and were not reported on the same day of vaccination or resolved within 1 day. The MAH's argumentation that the temporal

association, being predominantly 1 day after vaccination, is inconsistent with an infectious aetiology appears in principle plausible; but not a definite indicator, which would require further clinical information. Although the extent of true cellulitis reporting is uncertain, for 1 case of vaccination site abscess and, that concomitantly reported vaccination site cellulitis that appeared to have spread, an infectious agent was identified. The possible geographic reporting pattern and that no product quality issues for associated lots were identified is acknowledged. However, an at least reasonable possibility of a causal relationship with the administration procedure cannot be entirely excluded. Thus, from a conservative point of view, injection site cellulitis was included in the ADR table in section 4.8 of the SmPC under the SOC "General disorders and administration site conditions" with frequency "Not known". Frequency calculation of injection site cellulitis appears hampered based on available data due to uncertainties with regard to event classification. The rate of true cellulitis reporting based on post-marketing data is uncertain as well. Therefore, the proposed frequency "not known" is acceptable in this case for the time being. Further, the MAH agreed to monitor infections at the injection site and to provide updates based on event monitoring in the next PSUR submissions. Of note, the age of individuals reporting injection site infections was ≥12 months of age, except for one case affecting an 8-weeks old individual that however received a meningococcal vaccine from an unknown manufacturer.

2.5.2. Conclusions on clinical safety

The safety profile of MenACYW concomitantly administered with childhood vaccines as primary infant series followed by a toddler booster appears overall comparable to Menveo and Nimenrix, while only the latter comparator is approved in the EU for children below 12 months of age. Observed numerical differences between intervention groups are deemed not clinically meaningful. The majority of participants reported at least one vaccine-related AE. However, these events were mostly mild to moderate in intensity and resolved mainly within 3 days. The pattern and incidence of solicited reactions was largely comparable across subsequent infant doses and the booster dose, except for an increasing trend for fever between the first and subsequent doses.

The proportion of participants with SAE was overall comparable across comparator groups. The incidence of AESIs, including febrile convulsions/seizures (already included in the SmPC), was highest in the MenACYW group within 30-days after vaccination. However, only few were considered related and no new evidence as regards the risk thereof arose in this submission. The uncertainty concerning their unknown frequency remains.

From a clinical safety perspective this extension of indication is approvable.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 5.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 5.0 with the following content:

Safety concerns

Important identified risk	None
Important potential risk	None
Missing information	Use during pregnancy

Pharmacovigilance plan

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Pregnancy registry (MEQ00070) Ongoing	To assess maternal, obstetrical, pregnancy, and neonatal and infant outcomes among women vaccinated with MenACYW conjugate vaccine during pregnancy or in the 30 days preceding their last menstrual period or estimated date of conception.	Use during pregnancy	Planned submission of final study report	Q2 2029

Q: Quarter.

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Use during pregnancy	**Routine risk minimization measures:** SmPC section 4.6. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Pregnancy registry (MEQ00070)

SmPC: Summary of Product Characteristics.

2.7. Update of the Product information

As a consequence of this extension of the indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, and 5.1 of the SmPC have been updated. Particularly, new warnings with regard to indicate that infants who are

expected to be at increased risk of invasive meningococcal disease due to exposure to serogroup A, may be administered a 3-dose primary series, and to consider the potential risk of apnoea and the need for respiratory monitoring for 48-72 hours when administering the primary immunisation series to very premature infants (born ≤ 28 weeks of gestation), have been added to the product information. The Package Leaflet has been updated accordingly. The MAH is taking the opportunity to introduce editorial changes throughout the product information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The MAH applied to extend the indication for active immunisation against invasive meningococcal disease (IMD) caused by *Neisseria meningitidis* serogroups A, C, W, and Y to individuals starting from age of 6 weeks to below 12 months of age. Moreover, the MAH intended to amend the SmPC to include information concerning concomitant vaccination with routine childhood vaccines.

The virulence of *Neisseria meningitides* is mostly based on the biochemical structure of capsular polysaccharides. So far 12 distinct meningococcal serogroups have been classified, with serogroups A, B, C, W, X and Y being responsible for most cases of meningococcal disease. Dynamics of meningococcal transmission, acquisition, and carriage in humans are a major influence on the incidence and likelihood of meningococcal disease and vary world-wide greatly among regions. The European population is mostly affected by serogroup B, but also C and Y have been reported.

IMD is a serious, life-threatening disease, which clinically presents as septicaemia and meningitis. Seizures occur in approximately 20% of patients. In survivors, IMD can result in severe sequelae in 10% to 20% of patients despite appropriate therapy.

3.1.2. Available therapies and unmet medical need

Treatment

Treatment of IMD involves prompt recognition of disease and administration of antibiotics, usually beta-lactam antibiotics. However, despite prompt and adequate treatment, IMD still has a high rate of morbidity and mortality.

Prophylactic vaccines

Meningococcal vaccines induce the production of antibodies specific to the capsular polysaccharides of *N. meningitidis* serogroups, which protect against meningococcal diseases via complement mediated bactericidal activity.

In the EU the only quadrivalent meningococcal vaccine against serogroups A, C, W, and Y approved for individuals from the age of 6 weeks to below 12 months (and thus the population with the highest disease burden) is Nimenrix.

3.1.3. Main clinical studies

This application comprises data from 6 completed studies. None of those investigated efficacy, which is acceptable as a widely accepted immunological correlate of protection for meningococcal vaccines containing serogroups A, C, W and Y exists and this approach has also been used for approving the use of conjugated meningococcal vaccine Nimenrix in individuals from 6 weeks of age (Procedure No. EMEA/H/C/002226/II/0049). This is in line with relevant EMA Guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1) and WHO guidance (Annex 9, Guidelines on clinical evaluation of vaccines: regulatory expectations).

Immunogenicity and safety were investigated in 5 of those (MET58, MET33, MET52, MET42, and MET61), whereas one study (MET41) assessed safety only.

Study MET58 is considered as pivotal evidence, the remaining studies are considered to be of supportive value for concomitant vaccination. This is because among the provided studies, only study MET58 investigated comparison of MenQuadfi to Nimenrix whilst studies MET33, MET42, and MET61 applied MenACWY comparators (Menveo, Menactra) that are not approved in the EU for the relevant population (aged 6 weeks to 12 months). Study MET52 had no MenACWY comparator but investigated only concomitant vaccination with MenB vaccination (Bexsero).

3.2. Favourable effects

Based on the overall immunogenicity data, MenQuadfi elicited immune responses, including also anamnestic responses against all serogroups A, C, W, and Y. Immune responses measured by hSBA GMTs after the 3rd dose (booster dose after infancy), i.e. the primary analysis/PEP, and percentages of subjects with hSBA seroprotection titres (≥ 1:8) after the 2nd dose (last dose in infancy), i.e. the most important secondary analysis/SEP#1, which are of high relevance for meningococcal vaccines in infants, were of at least similar magnitude as the comparator Nimenrix for serogroups C, Y, and W:

- (PEP: 565 [95% CI: 505; 632] vs 120 [95% CI: 106; 135], 285 [95% CI: 260; 313] vs 160 [95% CI: 145; 177], 423 [95% CI: 382; 468] vs 275 [95% CI: 247; 305], for MenQuadfi vs Nimenrix, and serogroup C, Y, and W, respectively;
- SEP#1: 98.8% [95% CI: 97.5%; 99.6%] vs 91.9% [95% CI: 89.3%; 94.1%], 96.5% [95% CI: 94.5%; 97.9%] vs 93.5% [95% CI: 91.0%; 95.5%], 96.5% [95% CI: 94.6%; 97.9%] vs 94.5% [95% CI: 92.1%; 96.3%], for MenQuadfi vs Nimenrix, and serogroup C, Y, and W, respectively).

In addition, study results indicated that there is no interference of MenQuadfi administration on concomitant vaccination with routine childhood vaccine, namely the hexavalent DTaP-IPV-HB-Hib vaccines Hexyon or Hexacima, rotavirus vaccine (live attenuated) or Synflorix (PVC10).

3.3. Uncertainties and limitations about favourable effects

Although MenQuadfi elicited a certain level of antibody response against Serogroup A, titres similar to those elicited by the comparator Nimenrix were not achieved in the most relevant analyses (PEP: hSBA GMT at Day 30 after the 3rd dose: MenQuadfi: 131 [95% CI: 113; 151] vs Nimenrix: 189 [95% CI: 165; 218]; SEP#1: percentage of subjects with seroprotection titres (hSBA ≥ 1:8) at Day 30 after 2nd dose: MenQuadfi: 63.6% [95% CI: 59.2%; 67.8%] vs Nimenrix: 75.8 [95% CI: 71.8%; 79.5%]) and thus did not met non-inferiority. Moreover, all other data analyses were descriptively.

As regards the comparison of individuals with history of preterm birth to full-term birth, the sample size of those preterm was rather low and Study MET42 applied a 4-dose regimen (2, 4, 6 and 12

months), which impairs data interpretation. More importantly, no blood samples were taken after the 2nd dose and thus no immunogenicity analysis is available that would be required for comparison of immune responses (e.g., seroprotection rates) in infancy in accordance with the MAH's intended 2+1 dose regimen.

3.4. Unfavourable effects

The safety database comprises 6060 infants exposed to at least one dose of MenACYW and 4480 received at least 2 doses during infancy. In addition, 5373 toddlers were exposed to a booster dose after a primary infant series (1, 2 or 3 doses). The safety database is considered sufficiently large. The majority of safety database is informed by a 3+1 schedule and meningococcal vaccine administration was embedded in a vaccination scheme of other childhood vaccines.

Adverse events. The safety profile appears overall comparable to Menveo and Nimenrix. Across all studies, solicited injection site reactions and systemic reactions were the most commonly reported AEs. The vast majority of participants experienced at least 1 solicited adverse reaction after any dose of the primary infant series (86.8%) or the booster dose (74.5%). Thereof, 72.5% of participants in the MenACYW reported at least one solicited injection site reaction and 83.3% of participants in the MenACYW group reported at least one solicited systemic reaction after any dose. Irritability (74.6%), crying abnormal (66.2%) and drowsiness (61.7%) were the most frequently reported solicited reactions following any MenACYW dose. Injection site tenderness was the most frequently reported solicited injection site reaction (39.1%) after any dose. This pattern was comparable following any dose of the primary infant series and the booster dose, with a higher frequency following any infant dose. Event rates were largely consistent following each infant dose and the booster dose, with mostly a decreasing trend after dose 1 for solicited systemic reactions (any solicited systemic reaction dose 1: 71.1%, dose 2: 67.2%, dose 3: 62.0%). The exception was fever where a trend towards higher proportions of subjects reporting fever at subsequent vaccinations was observable after the first primary dose. Fever occurred in overall 32.2% of participants exposed to MenACYW (24.5% after any infant dose, 16.0% following the booster dose) and the frequency of Grade 3 fever (>39.5 °C) was in total low (1.6%). Solicited reactions were mostly Grade 1 to Grade 2 events and the majority resolved within 1-3 days.

Unsolicited AEs occurred in 59.5% participants following any dose. Unsolicited related AEs (ARs) were reported in 6.0% following any dose of the primary infant series and 4.9% after the booster dose (overall after any dose: 9.3%). Related events after any MenACYW dose were mostly linked to injection site reactions such as bruising (6.1%) and diarrhoea was the most frequently reported non-serious systemic ARs (0.6%). This was apparent after the primary infant series and the toddler booster dose, along with rash following the booster dose (0.2%). The majority of unsolicited ARs lasted 1-7 days and were mainly Grade 1 to Grade 2.

SAEs and Deaths. During the entire study duration and after any vaccine dose, 4.8% of participants in the MenACYW integrated group reported 386 SAEs, which was largely similar to the comparator groups. Most common SAEs concerned infections and febrile convulsions/seizures. Serious infections were slightly more frequently reported following any infant MenACYW dose compared to toddlers receiving the booster dose (within 7-days: 0.2% vs 0.1%, within 30-days: 0.9% vs 0.3%, entire study: 2.2% vs 0.7%), which mostly concerned LRTIs. A low number of SAEs were considered related. Four deaths were reported across the six integrated studies. All cases occurred in the MenACYW group, which were considered as not related.

AESIs. AESIs were reported at low rate in the MenACYW group (43 AESIs in 36/6060 participants, 0.6%) during the entire study, which was overall comparable to the other meningococcal vaccine

groups. All AESIs concerned generalised seizure except for one case of immune thrombocytopenia. Within 30-days after any vaccination, the 0.2% of participants reported an AESI and none in the comparator groups. One febrile convulsion was considered related to MenACYW by the Investigator but not the Sponsor. Three AESIs including 2 events of febrile convulsion and 1 event of seizure were reported within 7 days after any vaccine in the MenACYW arm.

Safety in special populations. Safety data from 237 preterm infants between 31-36 weeks gestational age at birth are available. Safety results were overall comparable between pre-term and full-term infants. Data on this age group is adequately reflected in the SmPC. A general warning as regards the potential risk of apnoea upon administering the primary immunisation series to very premature infants was included in section 4.4 of the SmPC, as already included in other authorised vaccines to be used in this age group.

Discontinuations due to AEs. 11 participants reported an AE leading to discontinuation within 30 days after any vaccination. Among the 8 participants with AEs leading to discontinuation in the MenACYW group, 2 experienced related AEs pertaining to injection site (tenderness, erythema, rash) and systemic reactions (fever, irritability and crying). The remaining AEs were considered not related and no accumulative pattern as regards a certain AE is evident.

3.5. Uncertainties and limitations about unfavourable effects

Comparative safety data. Safety data from Nimenrix (the only comparator approved in the EU for this age group) in the integrated safety summary is informed from 1 clinical study (MET58), in which the reporting frequency of solicited systemic reaction/AE/AR/SAE reporting rate was generally higher.

Safety of concomitant childhood vaccine administration. No control group with only childhood vaccines was largely included, limiting conclusions regarding potential differences between concomitant and separate vaccinations, especially applicable for systemic events.

SAE. Febrile convulsions and seizures are ADRs with unknown frequency.

3.6. Effects Table

Table 109: Effects Table for MenQuadfi EoI to individuals starting vaccination at 6 weeks of age

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Immunogenicity			MenQuadfi	Nimenrix		
Anti-Serogroup A, at Day 30 after 3rd dose	Dose 1 at 2 months of age, Dose 2 at 4 months of age, Dose 3 at 12-15 months of age	hSBA GMT	131 95% CI: 113; 151	189 95% CI: 165; 218	Unc/SoE: NI not met	MET58 CSR
Anti-Serogroup C, at Day 30 after 3rd dose	Dose 1 at 2 months of age, Dose 2 at 4 months of age, Dose 3 at 12-15 months of age	hSBA GMT	565 95% CI: 505; 632	120 95% CI: 106; 135	Unc/SoE: NI technically not met	MET58 CSR

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Anti-Serogroup W, at Day 30 after 3rd dose	Dose 1 at 2 months of age, Dose 2 at 4 months of age, Dose 3 at 12-15 months of age	hSBA GMT	285 95% CI: 260; 313	160 95% CI: 145; 177	Unc/SoE: NI technically not met	MET58 CSR
Anti-Serogroup Y, at Day 30 after 3rd dose	Dose 1 at 2 months of age, Dose 2 at 4 months of age, Dose 3 at 12-15 months of age	hSBA GMT	423 95% CI: 382; 468	275 95% CI: 247; 305	Unc/SoE: NI technically not met	MET58 CSR
Unfavourable Effects						
			MenACYW	Menveo/ Nimenrix	Unc: the only Nimenrix-controlled trial has a different reporting frequency compared to the integrated safety summary SoE: most commonly AEs following any dose concomitantly administered with routine childhood vaccines	Integrated summary of safety from 6 clinical trials evaluating a 1+1, 2+1 and 3+1 dosing schedule
Solicited Injection-site AE	Tenderness	%	64.6	65.3/58.3		
	Erythema	%	39.1	33.1/37.9		
	Swelling	%	25.5	22.8/21.6		
Solicited systemic AE	Irritability	%	74.6	70.1/86.1		
	Crying abnormal	%	66.2	61.3/82.1		
	Drowsiness	%	63.0	60.0/77.3		
Unsolicited ARs	Injection site reactions	%	7.7	6.0/10.5		
	Systemic reactions	%	2.0	0.9/8.9		

Abbreviations: Unc = Uncertainties, SoE = strength of evidence

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The presented data are indicative of immune responses, including also anamnestic responses, elicited by the meningococcal polysaccharide (serogroups A, C, W, and Y) tetanus toxoid conjugate vaccine MenQuadfi against all targeted serogroups. To contextualise these responses, comparison to Nimenrix, a meningococcal polysaccharide (serogroups A, C, W, and Y) tetanus toxoid conjugate vaccine EU-approved for individuals aged 6 weeks and older was investigated in the main, pivotal study MET58.

Immunogenicity was overall numerically higher (GMTs, seroprotection, seroresponse) in the MenQuadfi arm compared to the Nimenrix arm for serogroups C, W, and Y. In contrast, the primary analysis (hSBA GMT antibody response at Day 30 after the 3rd dose administered at 12-15 months of age) showed that serogroup A antibody titres of the MenQuadfi arm were significantly lower compared to Nimenrix. Therefore, since immune response with respect to the four investigated serotypes were considered co-primary implying that all four NI null hypotheses need to be rejected in order to make a claim on any one of them while controlling the multiple type I error, the primary objective to

demonstrate non-inferiority of MenQuadfi and Nimenrix as regards hSBA GMT antibody response at Day 30 after the 3rd dose was not achieved. Similarly, the only other pre-specified non-inferiority analysis (Secondary Objective #1, percentage of subjects with hSBA antibody titres >=1:8 (i.e., the threshold considered to confer seroprotection) at Day 30 after the second dose (i.e., 4-month vaccination) of MenQuadfi against the comparator Nimenrix) was not achieved (due to lower rates for serogroup A), and thus corroborated, together with other descriptive data, this finding.

The MAH argued that the clinical relevance of the observed differences in post-booster GMT levels for serogroup A is unknown as "there is no established minimum GMT level that correlates with individual-level protection against IMD" and "Although non-inferiority criteria were not met for serogroup A based on post-booster GMTs, other immune measures such as seroresponse, which is considered to be the most informative measure to estimate the actual effect of vaccine immune response, seroprotection, and analyses demonstrate that MenQuadfi is still likely to provide protection against serogroup A as well as against serogroups C, W, and Y following the 2+1 dosing schedule as vaccine seroresponse. In a post-hoc analysis, NI of the hSBA vaccine seroresponse rates after the booster dose was demonstrated for all 4 serogroups, including serogroup A. Additionally, the percentages of individuals with seroprotection (hSBA titre ≥ 1:8) post booster dose were close to 100% and comparable between MenACYW conjugate vaccine and Nimenrix for serogroups A, W, and Y, while the seroprotection rate for serogroup C was higher for MenACYW conjugate vaccine group." Concerning that, it is critically noted that the most relevant analysis is considered to be based on percentages with hSBA ≥ 1:8 (i.e., seroprotection rates) at one month after the last dose in infancy (as noted in scientific advice). This analysis was conducted by the MAH as Secondary Objective #1 but also did not successfully meet NI criteria. Additionally, although GMTs represent (only) the collective titres of the respective analysis group, this measure is in combination with other parameters considered informative for comparison of immunogenicity, and – noteworthy - the MAH chose GMTs for the primary analysis. Furthermore, as regards the post-hoc analysis of Study MET58 data (NI of the hSBA vaccine seroresponse rate at Day 30 after the 12 to 18-month vaccination compared to D0 before the 2-month vaccination), indeed, percentages were similar for all serogroups, however, albeit this is per se a relevant information, since the 3rd dose serves as booster to elicit anamnestic responses, such results are expected and thus comparison of seroresponse rates after the booster dose is less sensitive compared to GMTs (at Day 30 after the final dose) or other analyses after the 1st or 2nd dose.

Taken together, the most sensitive endpoint after the 3rd (booster) dose, i.e. GMT, as well as the most relevant endpoint from a clinical perspective, i.e. seroprotection after the 2nd (last infant) dose, failed to show non-inferior immune response against serogroup A.

Because of lower antibody titres against serogroup A observed after the second dose at 4 months of age when compared with Nimenrix, the CHMP considered that an additional primary (3rd) dose of MenQuadfi given at Month 6 of age may be considered necessary for infants who are expected to be at increased risk of invasive meningococcal disease due to exposure to serogroup A. These amendments were deemed appropriate to allow NITAGs to come up with recommendations for both the use of the vaccine and the vaccination regimen that is most applicable in certain epidemiological situations, lifestyle (e.g. travelling to areas with higher serogroup A incidence than in Europe) and certain risk groups.

Co-administration as regards the population aged 6 weeks to below 12 months of age was substantiated for the hexavalent vaccines Hexyon or Hexacima (Tetanus, Diphtheria, Pertussis, Poliovirus, Hepatitis B, *Haemophilus influenzae* type b [Hib]), rotavirus vaccine (live attenuated), and Synflorix (PCV10).

Concerning administration of MenQuadfi to infants with preterm birth history, the sample size of those preterm was rather low, the respective Study MET42 applied a 4-dose regimen (2, 4, 6 and 12

months) and most relevant blood samples after the 2nd dose were not taken, which all impairs data interpretation. Despite this limitation, information has been reflected adequately in the SmPC, allowing the same posology as infants born full term with an additional primary dose to be considered for some individuals in this population.

The safety profile of MenACYW was overall comparable to Menveo and Nimenrix, when co-administered with other childhood vaccines. Observed numerical differences are deemed not clinically meaningful. The latter comparison to the EU-approved comparator is limited as the only Nimenrix-controlled study MET58 generally had higher reporting frequencies of certain AEs in comparison to the integrated safety summary. However, no significant difference in the safety profile was noticeable also in Study MET58. Even though the majority of the safety database is informed by studies that employed a 3+1 dosing regimen, these data are seen relevant also for the safety of a 2+1 schedule. The vast majority of participants experienced at least one vaccine-related adverse event, which primarily entailed solicited adverse reactions. However, the pattern and frequency of solicited reactions was largely comparable following each infant dose and the booster dose, with mostly a decreasing trend for systemic solicited reactions. The frequency of fever trended higher with subsequent doses following dose 1 but the proportions of participants with Grade 3 fever remained <1%. In addition, the majority of AEs were Grade 1 to Grade 2 and of limited duration (≤3 days). The proportion of SAEs was overall comparable, with few AEs considered related. Although there were numerical differences between meningococcal vaccination groups in relation to serious infections, no concerning pattern of reported infections or time to onset was apparent after MenACYW administration. Observed numerical differences may be a chance finding. Febrile convulsions and seizures are important unfavourable effects but no new evidence regarding their risk arose.

3.7.2. Balance of benefits and risks

Considering the acceptable safety profile of MenQuadfi, the acceptable elicited immune response, and the recommendation for an additional (3rd) dose in the primary series of MenQuadfi given at Month 6 of age for infants who are expected to be at increased risk of invasive meningococcal disease due to exposure to serogroup A is reflected in the SmPC, a positive balance of benefits and risk for MenQuadfi in the population of those aged 6 weeks to <12 months can be concluded.

3.7.3. Additional considerations on the benefit-risk balance

None

3.8. Conclusions

The overall B/R of MenQuadfi is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or	Variation type II

	modification of an approved one	

Extension of indication for MenQuadfi to include the active immunisation of individuals from 6 weeks of age based on final results from study MET58 and additional supportive clinical studies. Study MET58 is a Phase 3, immunogenicity and safety study of MenQuadfi when administered concomitantly with routine paediatric vaccines in healthy infants and toddlers in Europe. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, and 5.1 of the SmPC have been updated. The Package Leaflet is updated in accordance. The MAH is taking the opportunity to include editorial changes throughout the product information. The Risk Management Plan (RMP) is also updated to version 5.0.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, IIIA and IIIB, and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric data

In this procedure, the CHMP reviewed the available data from the studies conducted in accordance with the agreed PIP P/0349/2024 namely studies MET33, MET41, MET42, MET52, MET58, MET61. As part of previous procedures, the CHMP also reviewed the data from the studies conducted in accordance with the agreed PIP, namely studies MET50, MET54, MET51, MET57, MET35, MET43, MET56, MET66 and MET59. The results of these studies are reflected in sections 4.8 and 5.1 of the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet. Further, these results were pivotal in supporting the new indication of

"MenQuadfi is indicated for active immunisation of individuals from the age of 6 weeks and older against invasive meningococcal disease caused by Neisseria meningitidis serogroups A, C, W, and Y.

The use of this vaccine should be in accordance with available official recommendations".