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

MenQuadfi

Meningococcal Group A, C, W and Y conjugate vaccine

Procedure no: EMEA/H/C/005084/P46/008

Note

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

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List of Abbreviations and Definitions of Terms

ABBREVIATIONS

AE	adverse event
AF	assent form
AESI	adverse event of special interest
AR	adverse reaction
BCP	business continuity plan
COVID-19	coronavirus disease 2019
CFR	Code of Federal Regulations
CI	confidence interval
CRF	case report form
CSR	clinical study report
D	Day
EEA	European Economic Area
EU	endotoxin units
EU	European Union
FAS	Full Analysis Set
FASC	Full Analysis Set for Concomitant vaccines
FPFV	first participant first visit
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GM	geometric mean
GMC	geometric mean concentration
GMR	geometric mean ratio
GMT	geometric mean titers
GMTR	geometric mean titers ratio
HIPAA	Health Insurance Portability and Accountability Act
HPV	human papilloma virus
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IMD	Invasive meningococcal disease
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	international units
LLOQ	lower limit of quantification
LPLV	last participant last visit
MedDRA	Medical Dictionary for Regulatory Activities
NIMP	non- investigational medicinal product
PPAS	Per-Protocol Analysis Set
PPASC	Per-Protocol Analysis Set for Concomitant vaccines
PPASM	Per-Protocol Analysis Set for Meningococcal vaccines
PT	preferred term
RCDCs	reverse cumulative distribution curves
SAE	serious adverse event
SafAS	overall safety analysis set
SAP	statistical analysis plan
SOC	System Organ Class
TESSy	European Surveillance System
WHO	World Health Organization

DEFINITION OF TERMS

FHA	filamentous hemagglutinin
FIM	fimbriae types 2 and 3
hSBA	human complement
PRN	pertactin
PT	pertussis toxoid
rSBA	baby rabbit complement

1. Introduction

On 06-Oct-2023, the MAH submitted a completed paediatric study MEQ00071 for MenQuadfi in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that MEQ00071 “A Phase IIIb study conducted in Spain, Italy, Hungary, and Singapore, was to compare MenACYW conjugate vaccine, a quadrivalent meningococcal conjugate vaccine with a licensed quadrivalent meningococcal polysaccharide (Groups A, C, W-135, Y) conjugate vaccine (Nimenrix®) in the adolescent population” is a stand-alone study. The MAH intends to submit a Type II variation with a Product Information update in Q1 2024 with the MEQ00071 study data.

2.2. Information on the pharmaceutical formulation used in the study

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

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study MEQ00071: Immunogenicity and Safety Study of a Quadrivalent Meningococcal Conjugate Vaccine Versus Nimenrix®, and When Administered Alone or Concomitantly with 9vHPV and Tdap-IPV Vaccines in Healthy Adolescents

2.3.2. Clinical study MEQ00071

Description

Study MEQ00071 is a IIIb immunogenicity and safety study conducted in Spain, Italy, Hungary, and Singapore, to compare MenACYW conjugate vaccine, a quadrivalent meningococcal conjugate vaccine with a licensed quadrivalent meningococcal polysaccharide (Groups A, C, W-135, Y) conjugate vaccine (Nimenrix®), when given alone or concomitantly with 9vHPV and Tdap-IPV Vaccines in Healthy Adolescents.

The study was conducted between 16 March 2021 (first subject enrolled) to 11 May 2022 (last subject last contact).

Methods

Study participants

Inclusion Criteria

Participants are eligible for the study only if all of the following criteria are met:

- I01: Aged 10 to 17 years on the day of inclusion (i.e., from the day of the 10th birthday to the day before the 18th birthday);
- I02: Meningococcal serogroup C conjugate vaccine (MenC) naïve participants or participants having received monovalent MenC priming in infancy (< 2 years of age) irrespective of the number of doses of MenC received in infancy;
- I03: Assent form has been signed and dated by the participant as per local regulation, and Informed Consent Form has been signed and dated by the parent/legally acceptable representative and by the participant if she/he turns 18 years old during the study;
- I04: Participant and parent/legally acceptable representative are able to attend all scheduled visits and to comply with all study procedures;
- I05: Covered by health insurance, if required by local regulations.

Exclusion Criteria

Participants are not eligible for the study if any of the following criteria are met:

- E01: Participant is pregnant, or lactating, or of childbearing potential and not using an effective method of contraception or abstinence from at least 4 weeks prior to vaccination until at least 4 weeks after last vaccination. To be considered of non-childbearing potential, a female must be pre-menarche;
- E02: Previous vaccination against meningococcal disease with either the study vaccine or another vaccine (i.e., polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C, W, or Y; or meningococcal B serogroup-containing vaccine), except licensed monovalent MenC vaccination received before 2 years of age;
- E03: Participation at the time of study enrollment (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;
- E04: Receipt of any vaccine in the 4 weeks preceding any study vaccination or planned receipt of any vaccine in the 4 weeks following any study vaccination except for influenza vaccination, which may be received at least 2 weeks before study vaccines. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines;
- E05: History of vaccination with any tetanus, diphtheria, pertussis, or inactivated polio virus vaccine within the previous 3 years;
- E06: Previous human papilloma virus (HPV) vaccination;
- E07: Receipt of immune globulins, blood or blood-derived products in the past 3 months;
- E08: Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months);
- E09: History of meningococcal infection, confirmed either clinically, serologically, or microbiologically;
- E10: Known history of diphtheria, tetanus, pertussis, poliomyelitis, and/or HPV infection or disease;
- E11: Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the study or to a vaccine containing any of the same substances;
- E12: Personal history of Guillain-Barré syndrome;
- E13: Personal history of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine within at least 10 years of the proposed study vaccination;
- E14: Personal history of new or past encephalopathy, progressive or unstable neurological disorder, or unstable epilepsy;

- E15: Verbal report of thrombocytopenia, contraindicating intramuscular vaccination;
- E16: Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination;
- E17: Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily;
- E18: Current alcohol abuse or drug addiction;
- E19: Chronic illness that, in the opinion of the Investigator, is at a stage where it may interfere with study conduct or completion;
- E20: Moderate or severe acute illness/infection (according to Investigator's judgment) on the day of vaccination or febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]). A prospective participant should not be included in the study until the condition has resolved or the febrile event has subsided;
- E21: Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw
- E22: Identified as an Investigator or employee of the Investigator or study centre with direct involvement in the proposed study, or identified as an immediate family member (i.e., parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study;
- E23: Participant at high risk for meningococcal infection during the study (specifically but not limited to participants with persistent complement deficiency, with anatomic or functional asplenia, or participants traveling to countries with high endemic or epidemic disease).

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

Table 1: Populations for Analyses

The following populations are defined:

Population	Description
Safety Analysis Set (SafAS)	Participants who have received at least one dose of the study vaccines[a] and have any safety data available. Three SafAS will be defined. ***Overall SafAS for any dose:*** Participants who have received at least one dose of the study vaccines[b] and have any safety data available. ***SafAS for vaccination at Visit 1 (SafAS1):*** Participants who have received at least one dose of the study vaccines[a] at Visit 1 (all groups) and have any safety data available. ***SafAS for vaccination at Visit 2 (SafAS2):*** Participants who have received at least one dose of the study vaccines[a] at Visit 2 (Group 1 and 2) and have any safety data available. For each SafAS, all participants will have their safety analyzed according to the study vaccine they actually received. Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).
Full analysis set (FAS)	Two FAS will be defined: one for hSBA measurement and one for rSBA measurement. ***hSBA FAS:***

	Subset of randomized participants who received at least one dose of the study vaccines and had a valid post-vaccination serology result. *rSBA FAS:* Subset of randomized participants who received at least one dose of the study vaccines and had a valid post-vaccination serology rSBA result. Participants will be analyzed according to the intervention to which they were randomized.
Per-protocol analysis sets (PPAS)	Subset of hSBA FAS and rSBA FAS. Three PPAS will be defined: two for meningococcal vaccines (hSBA PPASM and rSBA PPASM) and one for concomitant vaccines (PPASC). *hSBA and rSBA PPASM:* Participants presenting with at least 1 of the following relevant protocol deviations will be excluded from the hSBA and rSBA PPASM: • Participant did not meet all protocol-specified inclusion criteria or met at least 1 of the protocol-specified exclusion criteria • Participant did not receive the meningococcal vaccine • Participant received a vaccine other than the one that he/she was randomized to receive • Preparation and/or administration of vaccine was not done as per-protocol • Participant 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 (BL02AA or BL02AR) in Group 1 and 2: • Visit 2: Visit 1 + 30 days [+14 days] • Blood sampling 3 (BL03BB or BL03BR) in Group 3: • Visit 3: Visit 1 + 30 days [+14 days]

	• Participant received a protocol-prohibited therapy/medication /vaccine (Category 2 or Category 3) • Participant had other protocol violations that affected the participant's immune response, as determined by the clinical team before locking the database In addition, to the reasons listed above, participant will also be excluded from the *hSBA PPASM* if: • Participant serology samples did not produce a valid test result (ie, hSBA result for all meningococcal antigens are missing) And from *rSBA PPASM* if: • Participant serology samples did not produce a valid test result (ie, rSBA result for all meningococcal antigens are missing) *PPASC:* Participants presenting with at least 1 of the following relevant protocol deviations will be excluded from the PPASC: • Participant did not meet all protocol-specified inclusion criteria or met at least 1 of the protocol-specified exclusion criteria • Participant did not complete the vaccination schedule • Participant received a vaccine other than the one that he/she was randomized to receive • Preparation and/or administration of vaccine was not done as per-protocol • Participants did not receive the vaccine in the proper time window: • Visit 2: Visit 1 + 30 days [+14 days] (Group 1 and 2) • Participant did not provide a post-dose serology sample in the proper time window or a post-dose serology sample was not drawn: • Blood sampling 3 (BL03AA) in Group 1 and 2: • Visit 3: Visit 2 + 30 days [+14 days] • Blood sampling 3 (BL03BB or BL03BR) in Group 3:
	• Visit 3: Visit 1 + 30 days [+14 days] • Participant received a protocol-prohibited therapy/medication /vaccine (Category 2 or Category 3) • Participants with their serology samples that did not produce a valid test result (ie, results for all antigens contained in 9vHPV and Tdap-IPV vaccines are missing) • Participant had other protocol violations that affected the participant's immune response, as determined by the clinical team before locking the database In the event of a local or national immunization program (eg, with a pandemic influenza vaccine or COVID-19 vaccine), participants who receive 1 or more doses of pandemic influenza vaccine or COVID-19 vaccine at any time during the study will not be withdrawn from the study. If the participant receives the COVID-19 vaccine within this period of 28 days pre or post IMP vaccination (including the day of the study visit for IMP vaccine), she/he will be excluded from the PPAS population but will not be excluded from the study.

Treatments

Table 2: Overview of study interventions administered

Intervention Name	MenACYW conjugate vaccine: Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid	Nimenrix®: Meningococcal group A, C, W-135, and Y conjugate vaccine (Pfizer Limited,	9vHPV vaccine (Gardasil® 9): Human Papillomavirus 9-valent Vaccine (Recombinant, adsorbed) (Merck	Tdap-IPV vaccine (Repevax®/Triaxis® Polio/Adacel® Polio): Tetanus Toxoid, Reduced Diphtheria Toxoid and
	Conjugate Vaccine (Sanofi Pasteur Inc., Swiftwater, PA, USA)	Sandwich, United Kingdom)	Sharp & Dohme Limited, Kenilworth, NJ, USA)	Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliomyelitis Vaccine (Sanofi Pasteur Limited, Toronto, Ontario, Canada)
Use	Experimental	Active Comparator	Co-administered vaccine	Co-administered vaccine
IMP and NIMP	IMP	IMP	IMP	IMP
Type	Vaccine	Vaccine	Vaccine	Vaccine
Dose Formulation	Liquid solution	Powder and solvent for solution for injection	Suspension for injection	Suspension for injection

Unit Dose Strength	Meningococcal capsular polysaccharides:
	• Serogroup A 10 µg
	• Serogroup C 10 µg
	• Serogroup Y 10 µg
	• Serogroup W 10 µg
	Tetanus toxoid protein carrier approximately 55 µg*
	**Tetanus toxoid protein quantity is approximate and dependent on the polysaccharideto-protein ratio for the conjugates used in each formulation*
		• *N. meningitidis* group A polysaccharide * 5 µg
		• *N. meningitidis* group C polysaccharide * 5 µg
		• *N. meningitidis* group W-135 polysaccharide * 5 µg
		• *N. meningitidis* group Y polysaccharide * 5 µg
		**Conjugated to tetanus toxoid protein carrier 44 µg*
			• 30 µg of HPV 6 L1 protein
			• 40 µg of HPV 11 L1 protein
			• 60 µg of HPV 16 L1 protein
			• 40 µg of HPV 18 L1 Protein
			20 µg of HPV 31 L1 protein
			• 20 µg of HPV 33 L1 protein
			• 20 µg of HPV 45 L1 protein
			• 20 µg of HPV 52 L1 protein
			• 20 µg of HPV 58 L1 protein
			L1 protein in the form of virus-like particles produced in yeast cells (Saccharomyces cerevisiae CANA DE 3C-5 [Strain 1895]) by
				• Tetanus toxoid 5 Lf
				• Diphtheria toxoid 2 Lf
				• Acellular pertussis:
				  • PT 2.5 µg
				  • FHA 5 µg
				  • PRN 3 µg
				  • FIM 5 µg
				• Inactivated Poliomyelitis Vaccine
				  • Type 1 (Mahoney) 40 D-antigen units*
				  • Type 2 (MEF-1) 8 D-antigen units*
				  • Type 3 (Saukett) 32

			recombinant DNA technology. Adsorbed on amorphous aluminum hydroxyphosphate sulphate adjuvant (0.5 mg aluminum).	D-antigen units* ** Or the equivalent antigen quantity, determined by suitable immunochemical method* • Aluminum phosphate (adjuvant) 1.5 mg (0.33 mg aluminum)
Excipients/ Diluent	Sodium acetate buffered saline	Sucrose, trometamol, sodium chloride, and water for injections	Sodium chloride, L-histidine, polysorbate 80, sodium borate, and water for injections	• 2-phenoxyethanol 0.6% v/v • Polysorbate 80 < 5 µg (< 10 ppm) • Also contains traces of water for injection q.s. 0.5 mL Manufacturing Process Residuals Bovine serum albumin, formaldehyde, glutaraldehyde, polymyxin B, neomycin, and streptomycin are present in trace amounts.
Dosage Level	0.5 mL per dose	0.5 mL per dose	0.5 mL per dose	0.5 mL per dose
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection
Site of Administration	Deltoid muscle	Deltoid muscle	Deltoid muscle	Deltoid muscle
Sourcing	Provided by Sponsor	Provided by Sponsor	Provided by Sponsor	Provided by Sponsor
Packaging and Labeling	The study interventions, MenACYW conjugate vaccine (single dose vial), Nimenrix®, and other products were supplied with investigational labeling and packaging according to national regulations. Each single dose of study interventions was identified by a unique number on the detachable label and on the outer carton label. The detachable label was for the sites to attach to the source documents. See the Operating Guidelines for additional label detail.			
Current/Former Name or Alias	NA	NA	NA	NA
Batch Numbers	C1100201	C1100426	C1099228	C1100891

DNA: deoxyribo nucleic acid; FHA: filamentous hemagglutinin; FIM: fimbriae types 2 and 3; IMP: investigational medicinal product; Lf: limits of flocculation; NA: not applicable; NIMP: non-investigational medicinal product; ppm: part per million; PRN: pertactin; PT: pertussis toxoid; q.s.: quantity sufficient; v/v: volume/volume

The participants were randomised in a 3:3:2 ratio in the following study groups:

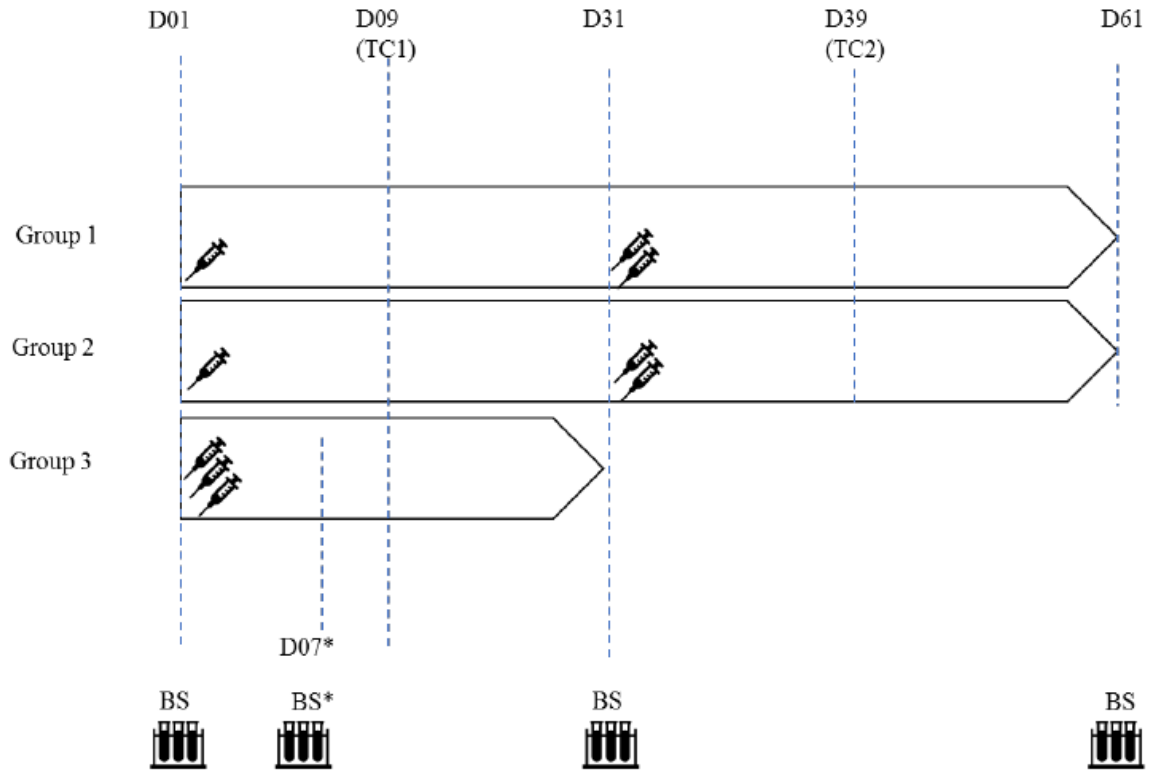
• Group 1 (investigational group – sequential administration): MenACYW conjugate vaccine on Day (D) 01 and 9vHPV* + Tdap-IPV vaccines on D31;

• Group 2 (control group – sequential administration): Nimenrix® on D01 and 9vHPV* + Tdap-IPV vaccines on D31;

• Group 3 (investigational group – concomitant administration): MenACYW conjugate vaccine + 9vHPV* + Tdap-IPV vaccines on D01.

*Note: This was the first dose of 9vHPV vaccine, of the 2-dose or 3-dose series according to the national recommendations and age of the participant. These additional vaccinations for the completion of 9vHPV vaccine schedule took place outside of the objectives and scope of this study.

Figure 1: Study design



BS: blood sample; D: day; TC: telephone call
*D07 visit and BS is applicable for a subset of participants (N=60) in Group 3. For this subset in Group 3, TC1 discussions can occur during Day 07 visit and TC1 is therefore optional.

Group 1: MenACYW conjugate vaccine on D01 + 9vHPV on D31 + Tdap-IPV on D31
Group 2: Nimenrix® on D01 + 9vHPV on D31 + Tdap-IPV on D31
Group 3: MenACYW conjugate vaccine + 9vHPV + Tdap-IPV on D01

Table 3: Schedule of vaccinations and blood draws for Groups 1 and 2

Visit					
	Visit 1 (D01)		Visit 2 (D31)		Visit 3 (D61)
Group	Blood Collection	Vaccination	Blood Collection	Vaccination	Blood Collection
1 (N=174)	BL1 (n=174)	MenACYW	BL2 (n=174)	9vHPVvaccine Tdap-IPV vaccine	BL3 (n=174)
2 (N=174)	BL1 (n=174)	Nimenrix®	BL2 (n=174)	9vHPV vaccine Tdap-IPV vaccine	BL3 (n=174)

Group 1: MenACYW conjugate vaccine on D01 and 9vHPV + Tdap-IPV vaccines on D31
Group 2: Nimenrix® on D01 and 9vHPV + Tdap-IPV vaccines on D31

Table 4: Schedule of vaccinations and blood draws for Group 3

	Visit			
	Visit 1 (D01)		Visit 2* (D07)	Visit 3 (D31)
Group	Blood Collection	Vaccination	Blood Collection	Blood Collection
3	BL1 (n=116)	MenACYW 9vHPVvaccine Tdap-IPV vaccine	BL2 (n=60)	BL3 (n=116)

Group 3: MenACYW conjugate vaccine + 9vHPV + Tdap-IPV vaccines on D01
*Visit at Day 07 was applicable only for a subset of participants, N=60. This subset had 3 blood samplings. All other participants in Group 3 had 2 study visits and 2 blood samplings.

Objective(s)

Primary Immunogenicity Objective

To demonstrate the non-inferiority of the seroprotection rate (serum bactericidal assay using human complement [hSBA] titer ≥ 1:8) to meningococcal serogroups A, C, W, and Y following the administration of a single dose of MenACYW conjugate vaccine (Group 1) compared to a single dose of Nimenrix (Group 2).

Secondary Immunogenicity Objectives

1. To describe the antibody response of meningococcal serogroups A, C, W, and Y measured by hSBA, before and 1 month following meningococcal vaccination administered alone (Groups 1 and 2) or concomitantly with 9vHPV and Tdap-IPV vaccines group (Group 3).
2. To describe the antibody response of meningococcal serogroup C measured by hSBA, before vaccination and at D31 after vaccination with the MenACYW conjugate vaccine or Nimenrix® (Groups 1 and 2) according to MenC primed status.
3. To describe the antibody response against antigens of 9vHPV and Tdap-IPV vaccines, before and 1 month following vaccination.

Safety Objective

To describe the safety profile in each group after each and any vaccination.

Outcomes/endpoints

Primary endpoint: Seroprotection against meningococcal serogroups A, C, W, and Y measured by hSBA titer ≥ 1:8 in Groups 1 and 2, on Day (D)31 (+14 days).

Besides the primary endpoint several secondary immunogenicity and safety endpoints as well as observational immunogenicity endpoints were pre-defined.

Table 5: Safety endpoints and time windows for collection Study MEQ00071

Safety Parameter	Data Collected and Collection Window
Immediate Unsolicited adverse events* (AEs)/adverse reactions (ARs)	0-30 minutes after vaccination by System Organ Class (SOC) and preferred term (PT)
Solicited (pre-defined) Injection Site Reactions	Within 7 days after vaccination (D01 to D08) by time of onset, number of days of occurrence, and maximum intensity
Solicited (pre-defined) Systemic Reactions	Within 7 days after vaccination (D01 to D08) by time of onset, number of days of occurrence, and maximum intensity
Unsolicited non-serious AEs/ARs	Within 30 days after vaccination (D01 to D31) by SOC and PT, time of onset, duration, and maximum intensity
Adverse Events of Special Interest (AESI)	All AESIs were collected throughout the trial as SAEs to ensure that the events are communicated to the Sponsor in an expedited manner and followed up until the end of the follow-up period or resolution, as per the assigned causality
Serious Adverse Events (SAE)s: All and related	SAEs were collected throughout the trial ensure that the events are communicated to the Sponsor in an expedited manner and followed up until the end of the follow-up period or resolution, as per the assigned causality
Deaths	Occurring throughout the trial period

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

The SafAS was defined as those subjects who had received at least one dose of the study vaccine(s) and had safety data available after any vaccination. For each SafAS, all participants had their safety analyzed according to the study vaccine they received.

Sample size

Approximately 464 participants were expected to be enrolled.

For the Primary Objective

With 174 enrolled participants in Group 1 and Group 2 each, the study will have a > 90% power (Farrington and Manning formula) to declare the non-inferiority of Group 1 versus Group 2 based on A, C, W, and Y hSBA antibody titers ≥ 1:8 (difference in the percentage of seroprotected participants in the 2 groups) after a single dose of MenACYW conjugate vaccine or Nimenrix®, assuming:

• A 10% dropout rate from the PPAS (155 participants evaluable per Group 1 and Group 2)

• A 1-sided alpha level of 2.5%

• A non-inferiority margin of 10% (percentage difference)

Table 6: Power of the study for the primary objective

Antigen	Estimated percentage of hSBA titer ≥ 1:8 MenACYW*	Non-inferiority margin†	Power
A	93.5%	10%	90.7%
C	98.5%	10%	> 99.9%
Y	97.2%	10%	99.3%
W	99.1%	10%	> 99.9%
Overall			≥ 90%

Since the hypothesis needs to be met for all serogroups, no alpha adjustment for multiple comparisons is necessary in these calculations.

* Percentages of participants with an hSBA titer ≥ 1:8 are based on the MET50 MenACYW (Group 1) post-dose result. The power is calculated with the assumption that the estimates from Group 1 equal that of Group 2 corresponding to the estimated percentages in Group 2 described above.

† A non-inferiority margin of 10% has been widely used in previous studies evaluating the same antigens and in a competitor's study of the same type. Also, considering the level of the reference rate taken in Group 2, it is reasonable to use 10%.

Randomisation and blinding (masking)

Randomisation and allocation Procedures

On the day of enrollment, participants who meet the inclusion/exclusion criteria, and who sign the Assent Form (AF) and whose parents/legally acceptable representatives sign the Informed Consent Form (ICF) will be randomly assigned to Groups 1, 2, or 3 in a 3:3:2 ratio.

The site staff will connect to the interactive response technology (IRT) system, enter the identification and security information, and confirm a minimal amount of data in response to IRT system prompts. The IRT system will then provide at least the participant number and vaccine group assignment. The IRT will also state whether the participant has been assigned to the D07 blood draw subset (first 60 participants of Group 3 only), and whether the participant will be in the rSBA testing subset (first 50 participants of each group). The full detailed procedures for group allocation are described in the Operating Guidelines. If the participant is not eligible to participate in the study, then the information will only be recorded on the participant recruitment log.

Blinding and Code-breaking Procedures

The study will be performed in a partially observer-blind fashion:

Groups 1 and 2 are observer-blind:

• Investigators and study staff who conduct the safety assessment, participants, parents/legally acceptable representatives, the Sponsor, and laboratory personnel performing the serology testing will be kept blinded to the vaccine received

• Only the study staff who prepare and administer the vaccine and are not involved with the safety evaluation will know which vaccine is administered

Group 3 is open-label:

• Everyone involved in the study (i.e., Investigator, study staff, the Sponsor, participants, parents/legally acceptable representatives) will know which vaccine is administered. This open-label design for Group 3 is due to the different vaccination schedule for this group than for Groups 1 and 2.

Statistical Methods

The primary objective will be met if the following null hypothesis is rejected for each of the 4 serogroup A, C, W, Y:

$$H_0: p_{\text{MenACYW}} - p_{Nimenrix} \leq -0.1$$
$$H_1: p_{\text{MenACYW}} - p_{Nimenrix} > -0.1$$

where p(MenACYW) and p(Nimenrix) are the percentages of participants who achieve an hSBA titer ≥ 1:8 in the MenACYW conjugate vaccine group and the comparator group (Nimenrix®), respectively.

The 95% confidence interval (CI) of the difference in proportion will be computed using the Wilson Score method without continuity correction (Newcombe method). If the lower limit of the 2-sided 95% CI of the difference between the 2 percentages is > -0.1, the non-inferiority will be demonstrated. Non-inferiority will be demonstrated if all 4 individual null hypotheses (4 serogroups) are rejected.

Results

Study participants

A total of 464 participants were planned to be enrolled, while a total of 463 participants were enrolled and randomised in this study: 173 participants were randomised to Groups 1 and 2 and 117 participants to Group 3.

Overall, there were 312 males (67.4%) and 151 females (32.6%) included. There were more males than females in all vaccination groups. There were 124 males (71.7%) and 49 females (28.3%) in Group 1, 116 males (67.1%) and 57 females (32.9%) in Group 2, and 72 males (61.5%) and 45 females (38.5%) in Group 3. The male/female ratio was 2.53 in Group 1, 2.04 in Group 2, and 1.60 in Group 3. Most participants were White (97.0%), followed by Asian participants (1.1%).

The mean age of participants was similar (12.6 years [±2.38]) in all vaccination groups.

Of the 462 randomised participants with a history of meningococcal C vaccination, 326 participants (70.4%) were previously vaccinated with meningococcal C vaccine (“MenC primed participants”) and 136 participants (29.4%) were not (“MenC naive participants”): MenC primed participants were 120 (69.4%) in Group 1, 119 (68.8%) in Group 2, and 87 (74.4%) in Group 3; MenC naive participants were 53 (30.6%) each in Groups 1 and 2, and 30 (25.6%) in Group 3.

Participant flow

Figure 2: Participant Disposition Flow Chart

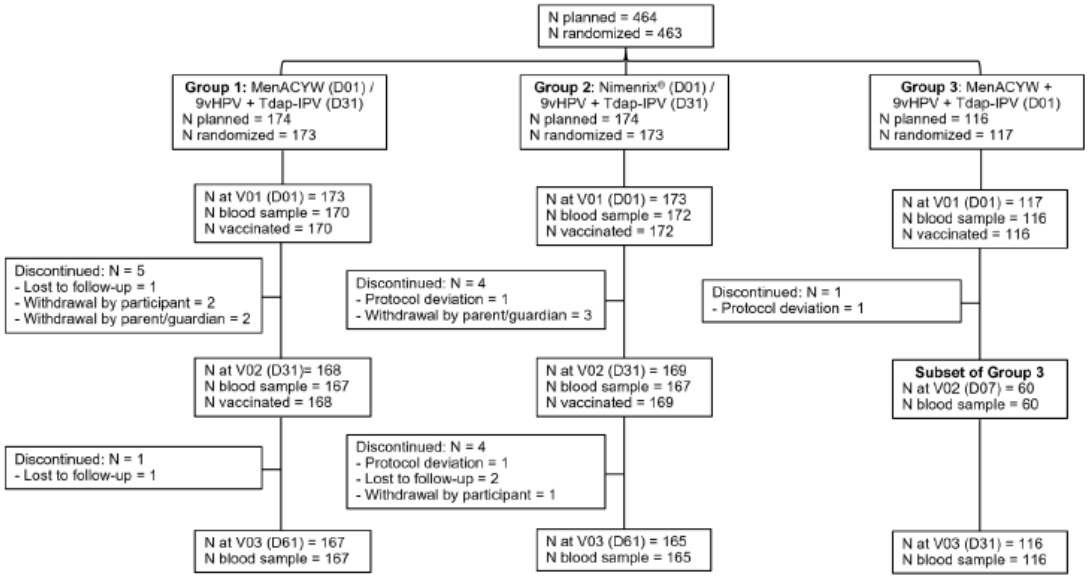


Table 7: The completion status of all participants by randomised group - Randomised Participants

	Group 1 (N=173) n (%)	Group 2 (N=173) n (%)	Group 3 (N=117) n (%)	All (N=463) n (%)
Completed	167 (96.5)	165 (95.4)	116 (99.1)	448 (96.8)
Early termination	6 (3.5)	8 (4.6)	1 (0.9)	15 (3.2)
Reason				
Adverse event*	0	0	0	0
Protocol deviation	0	2 (1.2)	1 (0.9)	3 (0.6)
Lost to follow-up	2 (1.2)	2 (1.2)	0	4 (0.9)
Withdrawal by participant	2 (1.2)	1 (0.6)	0	3 (0.6)
Withdrawal by parent/guardian	2 (1.2)	3 (1.7)	0	5 (1.1)

Group 1: MenACYW conjugate vaccine on D01 and 9vHPV + Tdap-IPV vaccines on D31.
Group 2: Nimenrix on D01 and 9vHPV + Tdap-IPV vaccines on D31.
Group 3: MenACYW conjugate vaccine + 9vHPV + Tdap-IPV vaccines on D01.
n: number of participants fulfilling the item listed
*Discontinuations for adverse events may not be considered at the time of the safety analysis if intensity is < Grade 1 according to the Sponsor.

Study Conduct

Table 8: Major or critical deviations by randomised group - Randomised Participants

	Group 1 (N=173) n (%)	Group 2 (N=173) n (%)	Group 3 (N=117) n (%)	All (N=463) n (%)
Participants with at least one major or critical protocol deviation	48 (27.7)	47 (27.2)	8 (6.8)	103 (22.2)
Participants with at least one major protocol deviation	48 (27.7)	47 (27.2)	8 (6.8)	103 (22.2)
E02: Previous vaccination against meningococcal disease with either study vaccine or other meningococcal vaccine, except licensed monovalent MenC vaccination received before 2 years of age	0	1 (0.6)	0	1 (0.2)
E04: Receipt of any vaccine in the 4 weeks preceding or following any study vaccination except for influenza vaccination, which may be received at least 2 weeks before study vaccines	1 (0.6)	0	1 (0.9)	2 (0.4)
E05: History of vaccination with any tetanus, diphtheria, pertussis, or inactivated polio virus vaccine within the previous 3 years	0	2 (1.2)	0	2 (0.4)
I02: Meningococcal serogroup C conjugate vaccine (MenC) naÃ¯ve participants or participants having received monovalent MenC priming in infancy (< 2 years of age)	1 (0.6)	2 (1.2)	2 (1.7)	5 (1.1)
IMP administered but not as per protocol	23 (13.3)	24 (13.9)	1 (0.9)	48 (10.4)
IMP administered but not within the protocol-specified time window	5 (2.9)	6 (3.5)	0	11 (2.4)
IMP kit number actually dispensed to the participant is different from the IMP kit number allocated	1 (0.6)	3 (1.7)	1 (0.9)	5 (1.1)
IMP not administered	3 (1.7)	1 (0.6)	1 (0.9)	5 (1.1)
IMP not fit for use but dispensed/administered	3 (1.7)	6 (3.5)	1 (0.9)	10 (2.2)
IRT randomization performed prior to participant visit	1 (0.6)	0	0	1 (0.2)
Missing or not provided safety participant's diary/ediary card	1 (0.6)	2 (1.2)	0	3 (0.6)
Participant randomized twice	0	1 (0.6)	0	1 (0.2)
Planned sample (blood) not performed within the protocol-specified time window at visit 1	1 (0.6)	0	1 (0.9)	2 (0.4)
Planned sample (blood) not performed within the protocol-specified time window at visit 2	0	0	1 (0.9)	1 (0.2)
Planned sample (blood) not performed within the protocol-specified time window at visit 3	7 (4.0)	7 (4.0)	0	14 (3.0)
Planned sample (blood) not performed at visit 1	3 (1.7)	0	1 (0.9)	4 (0.9)
Planned sample (blood) not performed at visit 2	1 (0.6)	2 (1.2)	0	3 (0.6)
Protocol prohibited therapy/medication/vaccine/ administered	5 (2.9)	2 (1.2)	1 (0.9)	8 (1.7)
Study Informed consent/Assent form obtained with a misconduct in consent process or documentation	4 (2.3)	1 (0.6)	0	5 (1.1)
Study physical visit, phone call or safety contact not performed	7 (4.0)	7 (4.0)	1 (0.9)	15 (3.2)
Study physical visit, phone call or safety contact not performed within the protocol-specified time window	11 (6.4)	14 (8.1)	3 (2.6)	28 (6.0)
Unappropriate treatment blinding management	2 (1.2)	1 (0.6)	0	3 (0.6)
Participants with at least one critical protocol deviation	4 (2.3)	1 (0.6)	0	5 (1.1)
IMP not fit for use but dispensed/administered	4 (2.3)	0	0	4 (0.9)
Planned sample (blood) not performed within the protocol-specified time window at visit 3[5]	0	1 (0.6)	0	1 (0.2)

Group 1: MenACYW conjugate vaccine on D01 and 9vHPV + Tdap-IPV vaccines on D31.
Group 2: Nimenrix on D01 and 9vHPV + Tdap-IPV vaccines on D31.
Group 3: MenACYW conjugate vaccine + 9vHPV + Tdap-IPV vaccines on D01.
n: number of participants experiencing the endpoint

The most frequently reported major protocol deviation was “IMP administered but not as per protocol” in 48 participants (10.4%). Indeed, 48 participants were wrongly administered with Tdap-IPV and/or 9vHPV vaccines in the same arm as MenACYW conjugate vaccine. One critical protocol deviation was reported in 4 participants (2.3%) in Group 1: “IMP not fit for use but dispensed/administered”.

Sensitivity Analyses based on study deviations

It was discovered during internal data review that 144 participants were wrongly enrolled with unblinding group data at Sponsor level. Thus, to assess the impact on safety data, the safety overview table excluding the prematurely unblinded participants will be displayed.

A recurring deviation has been detected during internal data reviews: some participants were wrongly administered with Tdap-IPV and/or 9vHPV in the same arm as MenACYW conjugate vaccine. To assess the impact on safety data, the safety overview, the solicited injection site and systemic reactions by duration, the summary of unsolicited AEs and unsolicited AEs by maximum intensity, time of onset and duration tables excluding the participants having received Tdap-IPV and/or 9vHPV in the same arm as MenACYW conjugate vaccine will be displayed.

Recruitment

Study period (first participant first visit to last participant last visit): 16 March 2021 to 11 May 2022.

The analyses presented in this report are based on a database lock date of 01 March 2023.

In total, the study was run at twenty-two study centres in Europe (Spain, Italy and Hungary) and in Asia (Singapore).

Baseline data

Table 9: Baseline demographic by randomised group - Randomised Participants

	Group 1 (N=173) n (%)	Group 2 (N=173) n (%)	Group 3 (N=117) n (%)	All (N=463) n (%)
Sex: n (%)				
Male	124 (71.7)	116 (67.1)	72 (61.5)	312 (67.4)
Female	49 (28.3)	57 (32.9)	45 (38.5)	151 (32.6)
Missing	0	0	0	0
Sex ratio: Male/Female	2.53	2.04	1.60	2.07
Age (years)				
M	173	173	117	463
Mean (SD)	12.4 (2.32)	12.8 (2.38)	12.5 (2.47)	12.6 (2.38)
Min ; Max	10.0 ; 17.0	10.0 ; 17.0	10.0 ; 17.0	10.0 ; 17.0
Median	11.0	12.0	11.0	12.0
Q1 ; Q3	11.0 ; 15.0	11.0 ; 15.0	11.0 ; 14.0	11.0 ; 15.0
Racial origin: n (%)				
White	165 (95.4)	169 (97.7)	115 (98.3)	449 (97.0)
Asian	2 (1.2)	2 (1.2)	1 (0.9)	5 (1.1)
Black	3 (1.7)	1 (0.6)	1 (0.9)	5 (1.1)
American Indian or Alaska Native	2 (1.2)	1 (0.6)	0	3 (0.6)
Native Hawaiian or Other Pacific Islander	0	0	0	0
Mixed origin	1 (0.6)	0	0	1 (0.2)
Unknown	0	0	0	0
Not Reported	0	0	0	0
Missing	0	0	0	0
If Asian : n (%)				
Chinese	1 (0.6)	2 (1.2)	1 (0.9)	4 (0.9)
Japanese	0	0	0	0
Asian Indian	0	0	0	0
Korean	0	0	0	0
Other Asian origin	1 (0.6)	0	0	1 (0.2)
Unknown	0	0	0	0
Not reported	0	0	0	0
Missing	0	0	0	0
Ethnicity: n (%)				
Hispanic or Latino	16 (9.2)	21 (12.1)	12 (10.3)	49 (10.6)
Not-Hispanic or Latino	157 (90.8)	152 (87.9)	105 (89.7)	414 (89.4)
Unknown	0	0	0	0
Not Reported	0	0	0	0
Missing	0	0	0	0
Country: n (%)				
Italy	34 (19.7)	35 (20.2)	21 (17.9)	90 (19.4)
Spain	75 (43.4)	75 (43.4)	52 (44.4)	202 (43.6)
Hungary	63 (36.4)	62 (35.8)	43 (36.8)	168 (36.3)
Singapore	1 (0.6)	1 (0.6)	1 (0.9)	3 (0.6)

Group 1: MenACYW conjugate vaccine on D01 and 9vHPV + Tdap-IPV vaccines on D31.
Group 2: Nimenrix on D01 and 9vHPV + Tdap-IPV vaccines on D31.
Group 3: MenACYW conjugate vaccine + 9vHPV + Tdap-IPV vaccines on D01.
n: number of participants fulfilling the item listed
M: number of participants with available data for the relevant endpoint
Q1; Q3: first quartile; third quartile

Of the 462 randomised participants with a history of meningococcal C vaccination, 326 participants (70.4%) were previously vaccinated with meningococcal C vaccine ("MenC primed participants") and 136 participants (29.4%) were not ("MenC naive participants"): MenC primed participants were 120 (69.4%) in Group 1, 119 (68.8%) in Group 2, and 87 (74.4%) in Group 3; MenC naive participants were 53 (30.6%) each in Groups 1 and 2, and 30 (25.6%) in Group 3.

Table 10: Numbers Analysed

Population	Number of Participants
Safety Analysis Set (SafAS)	Overall SafAS for any dose: 458 SafAS for vaccination at Visit 1 (SafAS1): 458 SafAS for vaccination at Visit 2 (SafAS2): 337
Full Analysis Set (FAS)	hSBA FAS: 450 rSBA FAS: 144 FASC: 448
Per-protocol analysis sets (PPAS) Per-Protocol Analysis Set for Meningococcal vaccines (PPASM) Per-Protocol Analysis Set for Concomitant vaccines (PPASC)	hSBA PPASM: 433 rSBA PPASM: 142 PPASC: 409

Table 11: Immunogenicity Analysis Sets for meningococcal vaccines by randomised group - Randomised Participants

	Group 1 (N=173) n (%)	Group 2 (N=173) n (%)	Group 3 (N=117) n (%)	All (N=463) n (%)
hSBA FAS	167 (96.5)	167 (96.5)	116 (99.1)	450 (97.2)
Not injected	3 (1.7)	1 (0.6)	1 (0.9)	5 (1.1)
Blood sample post-vaccination did not produce valid hSBA result*	6 (3.5)	6 (3.5)	1 (0.9)	13 (2.8)
hSBA PPASM	159 (91.9)	161 (93.1)	113 (96.6)	433 (93.5)
Participants with at least one deviation	14 (8.1)	12 (6.9)	4 (3.4)	30 (6.5)
Did not meet all protocol-specified inclusion/exclusion criteria	2 (1.2)	3 (1.7)	3 (2.6)	8 (1.7)
Did not receive the meningococcal vaccine	3 (1.7)	1 (0.6)	1 (0.9)	5 (1.1)
Received vaccine other than randomized	0	1 (0.6)	0	1 (0.2)
Vaccine not prepared/administered as per-protocol	0	0	0	0
Did not provide a post-dose serology sample†	3 (1.7)	5 (2.9)	0	8 (1.7)
Did not provide a post-dose serology sample in the proper time window†	4 (2.3)	3 (1.7)	2 (1.7)	9 (1.9)
Received protocol-prohibited therapy/medication/vaccine	5 (2.9)	2 (1.2)	1 (0.9)	8 (1.7)
Did not provide a valid blood test result (hSBA)†	6 (3.5)	6 (3.5)	1 (0.9)	13 (2.8)
Other protocol deviations	0	0	0	0
rSBA FAS‡	48 (96.0)	46 (92.0)	50 (100)	144 (96.0)
Not injected	1 (2.0)	0	0	1 (0.7)
Blood sample post-vaccination did not produce valid rSBA result*	2 (4.0)	4 (8.0)	0	6 (4.0)
rSBA PPASM‡	48 (96.0)	45 (90.0)	49 (98.0)	142 (94.7)
Participants with at least one deviation‡	2 (4.0)	5 (10.0)	1 (2.0)	8 (5.3)
Did not meet all protocol-specified inclusion/exclusion criteria	0	2 (4.0)	1 (2.0)	3 (2.0)
Did not receive the meningococcal vaccine	1 (2.0)	0	0	1 (0.7)
Received vaccine other than randomized	0	0	0	0
Vaccine not prepared/administered as per-protocol	0	0	0	0
Did not provide a post-dose serology sample†	1 (2.0)	4 (8.0)	0	5 (3.3)
Did not provide a post-dose serology sample in the proper time window†	0	0	0	0
Received protocol-prohibited therapy/medication/vaccine	0	0	0	0
Did not provide a valid blood test result (rSBA)†	2 (4.0)	4 (8.0)	0	6 (4.0)
Other protocol deviations	0	0	0	0

Group 1: MenACYW conjugate vaccine on D01 and 9vHPV + Tdap-IPV vaccines on D31. Group 2: Nimenrix on D01 and 9vHPV + Tdap-IPV vaccines on D31.
Group 3: MenACYW conjugate vaccine + 9vHPV + Tdap-IPV vaccines on D01.
n: number of participants fulfilling the item listed
FAS: Full Analysis Set; PPASM: Per-protocol analysis set for meningococcal vaccines
Note: A participant may be associated with more than 1 deviation.
*: i.e. results for all antigens equal to 'NR' or missing
† at V02 for Group 1 and Group 2 / V03 for Group 3 (D31)
‡ percentages are computed on the rSBA subset (N=150) instead of the Randomized participants.
Study: MEQ00071 Program: T08012.sas Datasets=ADSL ADIS Output: PRODOPS/PLC16012/MEQ00071/CSR_01/REPORT/OUTPUT/T08012_i.rtf (31MAR2023 14:45)

Efficacy results

For efficacy analyses, the hSBA Per-Protocol Analysis Set for Meningococcal vaccines (PPASM) is the most relevant analysis set.

Primary immunogenicity objective

Table 12: Non-inferiority of the antibody responses following the administration of a single dose of MenACYW conjugate vaccine compared to a single dose of Nimenrix (based on hSBA seroprotection rate)

	Serogroup	Group 1 (N=159)			Group 2 (N=161)			Group 1 minus Group 2				
Time point		n/M	%	(95% CI)*	n/M	%	(95% CI)*	Difference (%)	(95% CI)†	Delta (%)	Conclusion on non-inferiority	Overall non-inferiority
V02 (D31)	A	155/159	97.5	(93.7 ; 99.3)	148/160	92.5	(87.3 ; 96.1)	4.98	(0.06; 10.36)	-10.0	Yes	
	C	159/159	100	(97.7 ; 100)	153/161	95.0	(90.4 ; 97.8)	4.97	(1.58; 9.50)	-10.0	Yes	Yes
	W	159/159	100	(97.7 ; 100)	159/161	98.8	(95.6 ; 99.8)	1.24	(-1.28; 4.42)	-10.0	Yes	
	Y	157/158	99.4	(96.5 ; 100)	157/160	98.1	(94.6 ; 99.6)	1.24	(-1.88; 4.77)	-10.0	Yes	

Group 1: MenACYW conjugate vaccine on D01 and 9vHPV + Tdap-IPV vaccines on D31
Group 2: Nimenrix on D01 and 9vHPV + Tdap-IPV vaccines on D31
n: number of participants experiencing the endpoint listed in the first column; M: number of participants with available data for the relevant endpoint
Timepoint to consider: At V02 for Group 1 and Group 2
*95% CI of the single proportion calculated from the exact binomial method
†The two-sided 95% CI will be calculated based on the Wilson score method without continuity correction as described by Newcombe R.G.
The non-inferiority will be demonstrated if the lower limit of the 95% CI of the difference is greater than -10%.
Overall non-inferiority will be demonstrated if all 4 serotypes achieve non-inferiority

Secondary immunogenicity objectives

MenACWY response: MenQuadfi vs. Nimenrix

Table 13: Immune responses against meningococcal serogroups A, C, W, and Y 30 days after vaccination with meningococcal vaccines administered alone (hSBA PPASM)

Endpoint by Serogroup (hSBA-PPASM)	Group 1 (N=159)			Group 2 (N=161)		
GMTs	M	GMT	(95% CI)	M	GMT	(95% CI)
A	159	78.2	(64.6 ; 94.7)	160	56.0	(44.0 ; 71.2)
C	159	2294	(1675 ; 3142)	161	619	(411 ; 931)
W	159	134	(109 ; 164)	161	64.6	(52.5 ; 79.4)
Y	158	169	(141 ; 202)	160	84.8	(68.3 ; 105)
Seroresponse* %	n/M	%	(95% CI)	n/M	%	(95% CI)
A	139/158	88.0	(81.9 ; 92.6)	120/159	75.5	(68.0 ; 81.9)
C	157/158	99.4	(96.5 ; 100)	142/160	88.8	(82.8 ; 93.2)
W	148/159	93.1	(88.0 ; 96.5)	131/161	81.4	(74.5 ; 87.1)
Y	156/158	98.7	(95.5 ; 99.8)	141/160	88.1	(82.1 ; 92.7)

Group 1: MenACYW conjugate vaccine on D01 and 9vHPV + Tdap-IPV vaccines on D31
Group 2: Nimenrix on D01 and 9vHPV + Tdap-IPV vaccines on D31
N: number of participants in hSBA-PPASM for each group
n: number of participants experiencing the endpoint
M: number of participants with valid serology results for the particular time point
*hSBA vaccine seroresponse is defined as a post-vaccination titer >= 1:16 for participants with pre-vaccination hSBA titer < 1:8, or a post-vaccination titer >= 4-fold increase from baseline for participants with pre-vaccination hSBA titer >= 1:8

MenC response: MenC naive vs. primed

Table 14: Immune response for meningococcal serogroups C measured by hSBA

	Group 1						Group 2					
	MenC naive			MenC primed before 2 years of age			MenC naive			MenC primed before 2 years of age		
	N=45			N=114			N=49			N=112		
Seroprotection % ≥ 1:8	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
Serogroup C	45/45	100	(92.1 ; 100)	114/114	100	(96.8 ; 100)	42/49	85.7	(72.8 ; 94.1)	111/112	99.1	(95.1 ; 100)
GMTs	M	GMT	(95% CI)	M	GMT	(95% CI)	M	GMT	(95% CI)	M	GMT	(95% CI)
Serogroup C	45	489	(252 ; 949)	114	4222	(3166 ; 5632)	49	29.0	(17.5 ; 47.9)	112	2361	(1740 ; 3204)
Seroresponse* %	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
Serogroup C	45/45	100	(92.1 ; 100)	112/113	99.1	(95.2 ; 100)	32/49	65.3	(50.4 ; 78.3)	110/111	99.1	(95.1 ; 100)

Group 1: MenACYW conjugate vaccine on D01 and 9vHPV + Tdap-IPV vaccines on D31
Group 2: Nimenrix on D01 and 9vHPV + Tdap-IPV vaccines on D31
N: number of participants in hSBA-PPASM for each group
n: number of participants experiencing the endpoint listed
M: number of participants with valid serology for the relevant endpoint
*hSBA vaccine seroresponse is defined as a post-vaccination titer >= 1:16 for participants with pre-vaccination hSBA titer < 1:8, or a post-vaccination titer >= 4-fold increase from baseline for participants with pre-vaccination hSBA titer >= 1:8

Figure 3: Reverse cumulative distribution curves (RCDCs) of rSBA antibody titer against meningococcal serogroups - rSBA PPASM

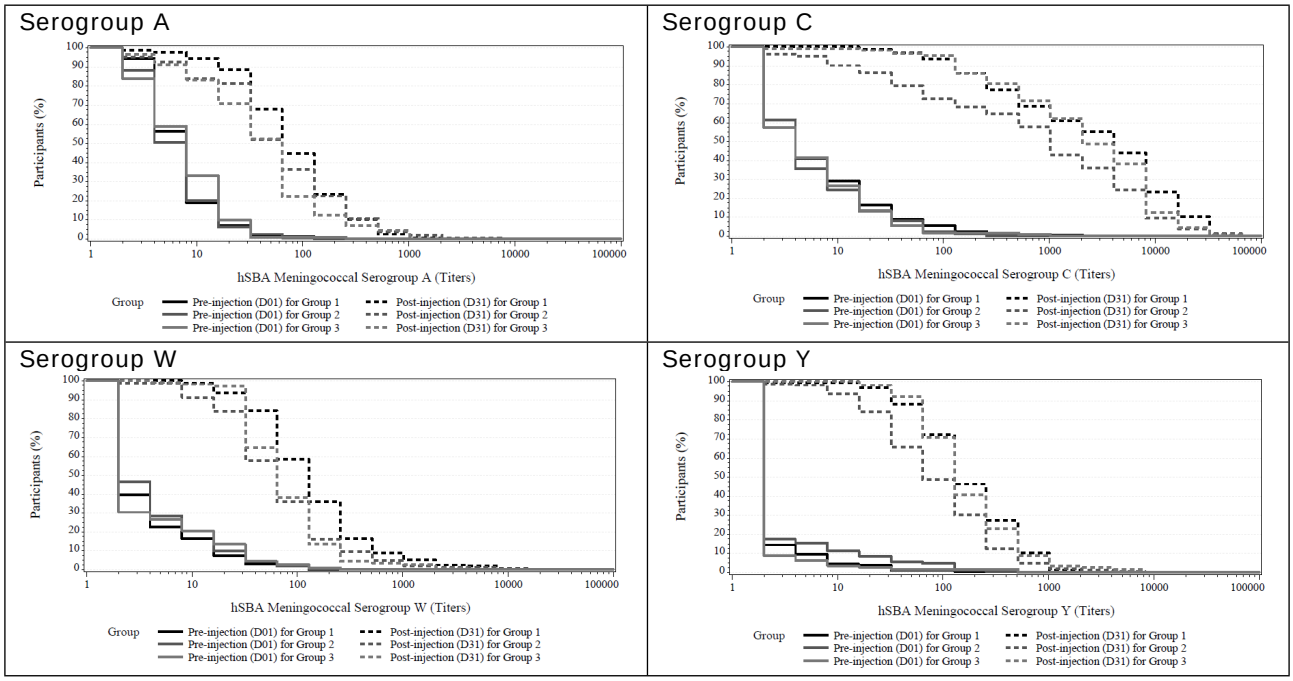
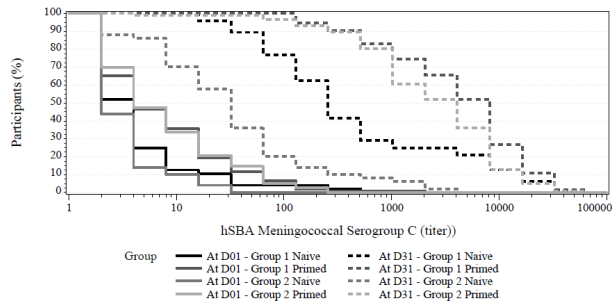


Figure 4: Reverse cumulative distribution curves (RCDCs) of hSBA antibody titer against meningococcal serogroup C according to MenC primed status - hSBA FAS



MenACWY response: MenQuadfi+9vHPV+TdapIPV (concomitantly vs. sequentially)

Table 15: Immune responses for meningococcal serogroups A, C, W, and Y 30 days after vaccination with MenACYW conjugate vaccine administered alone or concomitantly with 9vHPV + Tdap-IPV vaccines

Endpoint by Serogroup (hSBA-PPASM)	Group 1 (N=159)			Group 3 (N=113)		
Seroprotection % ≥ 1:8	n/M	%	(95% CI)	n/M	%	(95% CI)
A	155/159	97.5	(93.7 ; 99.3)	103/113	91.2	(84.3 ; 95.7)
C	159/159	100	(97.7 ; 100)	112/113	99.1	(95.2 ; 100)
W	159/159	100	(97.7 ; 100)	112/113	99.1	(95.2 ; 100)
Y	157/158	99.4	(96.5 ; 100)	113/113	100	(96.8 ; 100)
GMTs	M	GMT	(95% CI)	M	GMT	(95% CI)
A	159	78.2	(64.6 ; 94.7)	113	42.2	(32.5 ; 54.7)
C	159	2294	(1675 ; 3142)	113	1938	(1365 ; 2752)
W	159	134	(109 ; 164)	113	74.6	(61.8 ; 90.1)
Y	158	169	(141 ; 202)	113	171	(138 ; 211)
Seroresponse* %	n/M	%	(95% CI)	n/M	%	(95% CI)
A	139/158	88.0	(81.9 ; 92.6)	71/112	63.4	(53.8 ; 72.3)
C	157/158	99.4	(96.5 ; 100)	110/113	97.3	(92.4 ; 99.4)
W	148/159	93.1	(88.0 ; 96.5)	96/112	85.7	(77.8 ; 91.6)
Y	156/158	98.7	(95.5 ; 99.8)	112/113	99.1	(95.2 ; 100)

Group 1: MenACYW conjugate vaccine on D01 and 9vHPV + Tdap-IPV vaccines on D31
Group 3: MenACYW conjugate vaccine 9vHPV + Tdap-IPV vaccines on D01
N: number of participants in hSBA-PPASM for each group
n: number of participants experiencing the endpoint
M: number of participants with valid serology results for the particular time point
*hSBA vaccine seroresponse is defined as a post-vaccination titer >= 1:16 for participants with pre-vaccination hSBA titer < 1:8, or a post-vaccination titer >= 4-fold increase from baseline for participants with pre-vaccination hSBA titer >= 1:8

9vHPV response: MenQuadfi+9vHPV+TdapIPV (concomitantly vs. sequentially):

Table 16: Summary of geometric means of antibody titers against antigens contained in 9vHPV vaccine

		Group 1 (N=149)			Group 2 (N=147)			Group 3 (N=113)		
Component		M	GM/GMR	(95% CI)	M	GM/GMR	(95% CI)	M	GM/GMR	(95% CI)
Anti-HPV type-6 (mMU/mL)	Pre-Dose*	147	2.30	(1.94 ; 2.73)	147	2.03	(1.74 ; 2.37)	113	2.12	(1.76 ; 2.55)
	Post-Dose†	149	73.9	(64.3 ; 85.0)	147	64.8	(55.8 ; 75.4)	113	50.6	(42.0 ; 60.9)
	Post-Dose response based on pre-Dose	147	32.0	(26.5 ; 38.6)	147	31.9	(26.5 ; 38.5)	113	23.9	(19.4 ; 29.3)
Anti-HPV type-11 (mMU/mL)	Pre-Dose*	147	1.11	(1.05 ; 1.18)	147	1.08	(1.03 ; 1.13)	113	1.07	(1.02 ; 1.13)
	Post-Dose†	149	43.9	(38.9 ; 49.5)	147	39.3	(33.9 ; 45.5)	113	36.3	(30.8 ; 42.8)
	Post-Dose response based on pre-Dose	147	39.0	(34.2 ; 44.5)	147	36.5	(31.3 ; 42.7)	113	33.9	(28.6 ; 40.1)
Anti-HPV type-16 (mMU/mL)	Pre-Dose*	147	2.06	(1.95 ; 2.17)	147	2.08	(1.97 ; 2.19)	113	2.02	(1.98 ; 2.07)
	Post-Dose†	149	199	(171 ; 231)	147	168	(142 ; 199)	113	146	(118 ; 179)
	Post-Dose response based on pre-Dose	147	96.6	(83.4 ; 112)	147	80.8	(68.1 ; 95.8)	113	71.9	(58.6 ; 88.2)
Anti-HPV type-18 (mMU/mL)	Pre-Dose*	147	1.59	(1.50 ; 1.70)	147	1.52	(1.49 ; 1.54)	113	1.50	(NC ; NC)
	Post-Dose†	149	46.5	(38.4 ; 56.4)	147	38.5	(31.3 ; 47.4)	113	31.2	(24.0 ; 40.6)
	Post-Dose response based on pre-Dose	147	29.7	(24.4 ; 36.2)	147	25.4	(20.6 ; 31.2)	113	20.8	(16.0 ; 27.1)
Anti-HPV type-31 (mMU/mL)	Pre-Dose*	147	1.08	(0.995 ; 1.18)	147	1.05	(1.01 ; 1.10)	113	1.07	(1.02 ; 1.13)
	Post-Dose†	149	31.7	(26.5 ; 38.1)	147	28.9	(24.0 ; 34.9)	113	24.7	(19.2 ; 31.8)
	Post-Dose response based on pre-Dose	147	29.8	(25.1 ; 35.4)	147	27.5	(22.8 ; 33.2)	113	23.1	(17.9 ; 29.6)
Anti-HPV type-33 (mMU/mL)	Pre-Dose*	147	1.01	(0.987 ; 1.04)	147	1.02	(0.997 ; 1.04)	113	1.01	(0.989 ; 1.03)
	Post-Dose†	149	21.1	(17.8 ; 24.9)	147	19.1	(16.1 ; 22.7)	113	15.0	(12.2 ; 18.6)
	Post-Dose response based on pre-Dose	147	20.8	(17.7 ; 24.4)	147	18.7	(15.8 ; 22.2)	113	14.9	(12.0 ; 18.4)
Anti-HPV type-45 (mMU/mL)	Pre-Dose*	147	0.520	(0.499 ; 0.543)	147	0.509	(0.492 ; 0.527)	113	0.524	(0.493 ; 0.556)
	Post-Dose†	149	11.5	(9.35 ; 14.1)	147	9.54	(7.68 ; 11.9)	113	8.24	(6.30 ; 10.8)

	Post-Dose response based on pre-Dose	147	21.9	(17.9 ; 26.9)	147	18.8	(15.1 ; 23.3)	113	15.7	(12.0 ; 20.7)
Anti-HPV type-52 (mMU/mL)	Pre-Dose*	147	0.535	(0.503 ; 0.569)	147	0.514	(0.498 ; 0.530)	113	0.521	(0.500 ; 0.544)
	Post-Dose†	149	47.4	(41.1 ; 54.7)	147	39.3	(33.5 ; 46.1)	113	40.9	(33.5 ; 49.8)
	Post-Dose response based on pre-Dose	147	88.0	(77.1 ; 100)	147	76.5	(65.0 ; 90.1)	113	78.4	(64.3 ; 95.5)
Anti-HPV type-58 (mMU/mL)	Pre-Dose*	147	1.09	(1.02 ; 1.16)	147	1.05	(1.00 ; 1.10)	113	1.08	(1.02 ; 1.14)
	Post-Dose†	149	29.6	(25.5 ; 34.3)	147	26.0	(22.2 ; 30.4)	113	20.6	(16.9 ; 25.1)
	Post-Dose response based on pre-Dose	147	27.1	(23.3 ; 31.4)	147	24.8	(21.2 ; 29.0)	113	19.1	(15.8 ; 23.2)

Group 1: MenACYW conjugate vaccine on D01 and 9vHPV + Tdap-IPV vaccines on D31. Group 2: Nimenrix on D01 and 9vHPV + Tdap-IPV vaccines on D31
Group 3: MenACYW conjugate vaccine + 9vHPV + Tdap-IPV vaccines on D01
M: number of participants with available data for the relevant endpoint
* at V02 for Group 1 and Group 2 (D31) and at V01 for Group 3 (D01)
† at V03 for Group 1 and Group 2 (D61) and at V03 for Group 3 (D31)

Table 17: Seroconversion of antibody titers against antigens contained in HPV - PPASC

		Group 1 (N=149)			Group 2 (N=147)			Group 3 (N=113)		
Component	**Criteria**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Anti-HPV type-6 (mMU/mL)	Seroconversion*	129/147	87.8	(81.3 ; 92.6)	130/147	88.4	(82.1 ; 93.1)	96/113	85.0	(77.0 ; 91.0)
Anti-HPV type-11 (mMU/mL)	Seroconversion*	146/147	99.3	(96.3 ; 100)	143/147	97.3	(93.2 ; 99.3)	110/113	97.3	(92.4 ; 99.4)
Anti-HPV type-16 (mMU/mL)	Seroconversion*	146/147	99.3	(96.3 ; 100)	142/147	96.6	(92.2 ; 98.9)	111/113	98.2	(93.8 ; 99.8)
Anti-HPV type-18 (mMU/mL)	Seroconversion*	139/147	94.6	(89.6 ; 97.6)	136/147	92.5	(87.0 ; 96.2)	100/113	88.5	(81.1 ; 93.7)
Anti-HPV type-31 (mMU/mL)	Seroconversion*	142/147	96.6	(92.2 ; 98.9)	137/147	93.2	(87.8 ; 96.7)	100/113	88.5	(81.1 ; 93.7)
Anti-HPV type-33 (mMU/mL)	Seroconversion*	140/147	95.2	(90.4 ; 98.1)	135/147	91.8	(86.2 ; 95.7)	99/113	87.6	(80.1 ; 93.1)
Anti-HPV type-45 (mMU/mL)	Seroconversion*	120/147	81.6	(74.4 ; 87.5)	122/147	83.0	(75.9 ; 88.7)	85/113	75.2	(66.2 ; 82.9)
Anti-HPV type-52 (mMU/mL)	Seroconversion*	146/147	99.3	(96.3 ; 100)	144/147	98.0	(94.2 ; 99.6)	109/113	96.5	(91.2 ; 99.0)
Anti-HPV type-58 (mMU/mL)	Seroconversion*	140/147	95.2	(90.4 ; 98.1)	136/147	92.5	(87.0 ; 96.2)	104/113	92.0	(85.4 ; 96.3)

Group 1: MenACYW conjugate vaccine on D01 and 9vHPV + Tdap-IPV vaccines on D31. Group 2: Nimenrix on D01 and 9vHPV + Tdap-IPV vaccines on D31.
Group 3: MenACYW conjugate vaccine + 9vHPV + Tdap-IPV vaccines on D01.
n: number of participants experiencing the endpoint listed in the first two columns
M: number of participants with available data for the relevant endpoint
* Changing serostatus from seronegative at baseline to seropositive after vaccination.
A participant with a titer at or above the serostatus cut-off for a given HPV type is considered seropositive for that type.
The serostatus cut-offs for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 are 9, 6, 5, 5, 3, 4, 3, 5 and 5 milli-Merck units (mMU)/mL, respectively

Tdap-IPV response: MenQuadfi+9vHPV+TdapIPV (concomitantly vs. Sequentially):

Table 18: Summary of geometric means of antibody concentration/titers against antigens contained in Tdap-IPV vaccine

		Group 1 (N=149)			Group 2 (N=147)			Group 3 (N=113)		
Component		**M**	**GM/GMR**	**(95% CI)**	**M**	**GM/GMR**	**(95% CI)**	**M**	**GM/GMR**	**(95% CI)**
Anti-Tetanus (IU/mL)	Pre-Dose*	147	25.5	(22.0 ; 29.5)	147	18.4	(15.8 ; 21.5)	113	0.708	(0.574 ; 0.874)
	Post-Dose†	149	17.3	(14.9 ; 20.1)	147	16.1	(14.1 ; 18.5)	113	34.5	(30.1 ; 39.6)
	Post-Dose response based on pre-Dose	147	0.677	(0.646 ; 0.710)	147	0.876	(0.824 ; 0.931)	113	48.7	(40.1 ; 59.3)
Anti-Diphtheria (IU/mL)	Pre-Dose*	147	0.200	(0.169 ; 0.238)	147	0.215	(0.181 ; 0.254)	113	0.256	(0.208 ; 0.316)
	Post-Dose†	149	3.75	(3.24 ; 4.35)	147	3.88	(3.37 ; 4.47)	113	2.91	(2.46 ; 3.44)
	Post-Dose response based on pre-Dose	147	18.5	(15.3 ; 22.5)	147	18.1	(15.1 ; 21.7)	113	11.4	(9.17 ; 14.1)
Anti-Polio type 1 (titer)	Pre-Dose*	147	94.7	(75.5 ; 119)	146	109	(86.0 ; 138)	113	146	(112 ; 190)
	Post-Dose†	149	3135	(2692 ; 3650)	147	3266	(2778 ; 3840)	113	1593	(1306 ; 1943)
	Post-Dose response based on pre-Dose	147	32.9	(24.5 ; 44.2)	146	29.5	(22.1 ; 39.4)	113	10.9	(7.77 ; 15.4)
Anti-Polio type 2 (titer)	Pre-Dose*	147	227	(184 ; 281)	147	234	(188 ; 292)	113	225	(178 ; 285)
	Post-Dose†	147	3344	(2635 ; 4245)	147	2648	(2074 ; 3381)	113	2950	(2409 ; 3613)
	Post-Dose response based on pre-Dose	145	14.9	(10.8 ; 20.5)	147	11.3	(8.09 ; 15.8)	113	13.1	(9.66 ; 17.8)
Anti-Polio type 3 (titer)	Pre-Dose*	147	135	(105 ; 174)	147	155	(120 ; 200)	113	221	(162 ; 302)
	Post-Dose†	149	7059	(5861 ; 8502)	147	5591	(4647 ; 6728)	113	3166	(2553 ; 3926)
	Post-Dose response based on pre-Dose	147	51.8	(38.0 ; 70.5)	147	36.1	(26.7 ; 48.8)	113	14.3	(10.1 ; 20.3)
Anti-PT (EU/mL)	Pre-Dose*	145	11.9	(10.2 ; 13.8)	147	12.3	(10.5 ; 14.4)	113	8.77	(7.07 ; 10.9)
	Post-Dose†	149	58.4	(50.6 ; 67.4)	147	59.3	(51.1 ; 68.8)	113	41.4	(36.1 ; 47.4)
	Post-Dose response based on pre-Dose	145	4.90	(4.36 ; 5.51)	147	4.83	(4.33 ; 5.38)	113	4.72	(4.05 ; 5.49)
Anti-FHA (EU/mL)	Pre-Dose*	147	47.3	(40.9 ; 54.7)	147	58.3	(51.4 ; 66.1)	113	44.5	(37.5 ; 52.9)
	Post-Dose†	149	177	(156 ; 200)	147	210	(187 ; 236)	113	146	(128 ; 166)
	Post-Dose response based on pre-Dose	147	3.76	(3.24 ; 4.35)	147	3.61	(3.18 ; 4.09)	113	3.27	(2.82 ; 3.80)

Anti-PRN (EU/mL)	Pre-Dose*	147	14.5	(11.2 ; 18.8)	147	18.2	(14.0 ; 23.7)	113	11.4	(8.40 ; 15.6)
	Post-Dose†	149	331	(265 ; 414)	147	394	(316 ; 491)	113	236	(184 ; 303)
	Post-Dose response based on pre-Dose	147	22.4	(17.9 ; 27.9)	147	21.6	(16.9 ; 27.7)	113	20.6	(15.7 ; 27.1)
Anti-FIM (EU/mL)	Pre-Dose*	147	2.74	(2.23 ; 3.37)	147	3.18	(2.56 ; 3.95)	113	2.32	(1.84 ; 2.94)
	Post-Dose†	149	152	(112 ; 207)	147	194	(140 ; 271)	113	106	(75.3 ; 149)
	Post-Dose response based on pre-Dose	147	55.3	(44.4 ; 68.9)	147	61.2	(49.4 ; 75.8)	113	45.7	(35.7 ; 58.5)

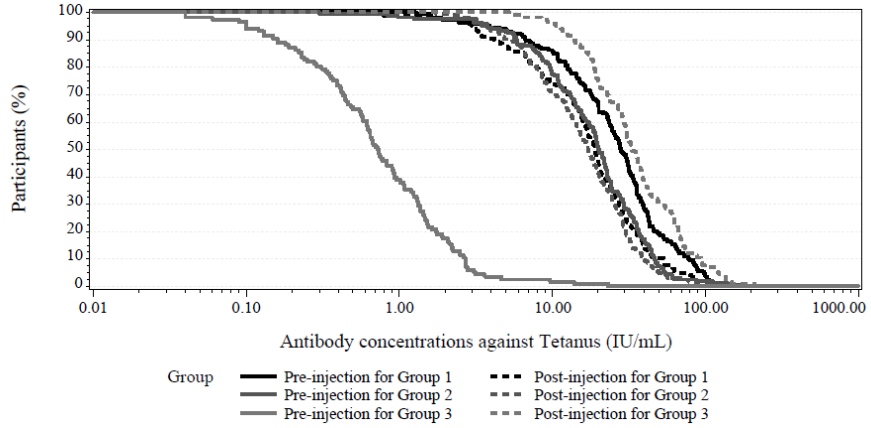
Group 1: MenACYW conjugate vaccine on D01 and 9vHPV + Tdap-IPV vaccines on D31
Group 2: Nimenrix on D01 and 9vHPV + Tdap-IPV vaccines on D31
Group 3: MenACYW conjugate vaccine + 9vHPV + Tdap-IPV vaccines on D01
M: number of participants with available data for the relevant endpoint
* at V02 for Group 1 and Group 2 (D31) and at V01 for Group 3 (D01)
† at V03 for Group 1 and Group 2 (D61) and at V03 for Group 3 (D31)

Table 19: Summary of response rates of antibody concentrations/Titers against antigens contained in Tdap-IPV - PPASC

			Group 1 (N=149)			Group 2 (N=147)			Group 3 (N=113)		
Component	**Time point**	**Criteria**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Anti-Tetanus (IU/mL)	Pre-Dose*	>= 0.1 IU/mL	147/147	100	(97.5 ; 100)	147/147	100	(97.5 ; 100)	109/113	96.5	(91.2 ; 99.0)
		>= 1.0 IU/mL	147/147	100	(97.5 ; 100)	144/147	98.0	(94.2 ; 99.6)	44/113	38.9	(29.9 ; 48.6)
	Post-Dose†	>= 0.1 IU/mL	149/149	100	(97.6 ; 100)	147/147	100	(97.5 ; 100)	113/113	100	(96.8 ; 100)
		>= 1.0 IU/mL	148/149	99.3	(96.3 ; 100)	147/147	100	(97.5 ; 100)	113/113	100	(96.8 ; 100)
Anti-Diphteria (IU/mL)	Pre-Dose*	>= 0.1 IU/mL	113/147	76.9	(69.2 ; 83.4)	117/147	79.6	(72.2 ; 85.8)	96/113	85.0	(77.0 ; 91.0)
		>= 1.0 IU/mL	7/147	4.8	(1.9 ; 9.6)	7/147	4.8	(1.9 ; 9.6)	11/113	9.7	(5.0 ; 16.8)
	Post-Dose†	>= 0.1 IU/mL	149/149	100	(97.6 ; 100)	147/147	100	(97.5 ; 100)	112/113	99.1	(95.2 ; 100)
		>= 1.0 IU/mL	139/149	93.3	(88.0 ; 96.7)	136/147	92.5	(87.0 ; 96.2)	102/113	90.3	(83.2 ; 95.0)
Anti-Polio type 1 (titer)	Pre-Dose*	>=1:8	140/147	95.2	(90.4 ; 98.1)	139/146	95.2	(90.4 ; 98.1)	112/113	99.1	(95.2 ; 100)
	Post-Dose†	>=1:8	149/149	100	(97.6 ; 100)	147/147	100	(97.5 ; 100)	113/113	100	(96.8 ; 100)
Anti-Polio type 2 (titer)	Pre-Dose*	>=1:8	146/147	99.3	(96.3 ; 100)	147/147	100	(97.5 ; 100)	113/113	100	(96.8 ; 100)
	Post-Dose†	>=1:8	147/147	100	(97.5 ; 100)	147/147	100	(97.5 ; 100)	113/113	100	(96.8 ; 100)
Anti-Polio type 3 (titer)	Pre-Dose*	>=1:8	141/147	95.9	(91.3 ; 98.5)	142/147	96.6	(92.2 ; 98.9)	109/113	96.5	(91.2 ; 99.0)
	Post-Dose†	>=1:8	149/149	100	(97.6 ; 100)	147/147	100	(97.5 ; 100)	113/113	100	(96.8 ; 100)
Anti-PT (EU/mL)	Post-Dose response based on pre-Dose	Seroresponse‡	118/145	81.4	(74.1 ; 87.4)	122/147	83.0	(75.9 ; 88.7)	86/113	76.1	(67.2 ; 83.6)
Anti-FHA (EU/mL)	Post-Dose response based on pre-Dose	Seroresponse‡	110/147	74.8	(67.0 ; 81.6)	112/147	76.2	(68.5 ; 82.8)	80/113	70.8	(61.5 ; 79.0)
Anti-PRN (EU/mL)	Post-Dose response based on pre-Dose	Seroresponse‡	144/147	98.0	(94.2 ; 99.6)	139/147	94.6	(89.6 ; 97.6)	103/113	91.2	(84.3 ; 95.7)
Anti-FIM (EU/mL)	Post-Dose response based on pre-Dose	Seroresponse‡	138/147	93.9	(88.7 ; 97.2)	143/147	97.3	(93.2 ; 99.3)	108/113	95.6	(90.0 ; 98.5)

Group 1: MenACYW conjugate vaccine on D01 and 9vHPV + Tdap-IPV vaccines on D31. Group 2: Nimenrix on D01 and 9vHPV + Tdap-IPV vaccines on D31.
Group 3: MenACYW conjugate vaccine + 9vHPV + Tdap-IPV vaccines on D01.
n: number of participants experiencing the endpoint listed in the first three columns
M: number of participants with available data for the relevant endpoint
* at V02 for Group 1 and Group 2 (D31) and at V01 for Group 3 (D01)
† at V03 for Group 1 and Group 2 (D61) and at V03 for Group 3 (D31)
‡ Seroresponse is defined as post-vaccination concentration >= 4 × baseline concentration, if the anti-pertussis antibody concentration at baseline is < 4 × LLOQ, or >= 2 × baseline concentration, if the anti-pertussis antibody concentration at baseline is >= 4 × LLOQ.
Study: MEQ00071 Program: T08126toT08127.sas Datasets=ADSL ADIS Output: PRODOPS/PLC16012/MEQ00071/CSR_01/REPORT/OUTPUT/T08126_i.rtf (31MAR2023 14:46)

Figure 5: Reverse cumulative distribution curves (RCDCs) of antibody concentrations against Tetanus (IU/mL) – FASC



Safety results

Extent of exposure:

A total of 463 participants were enrolled and randomised in the study: 173 participants were randomised to Group 1, 173 participants were randomised to Group 2, and 117 participants were randomised to Group 3.

At Visit 1, in Group 1, 170 participants (98.3%) received the MenACYW conjugate vaccine, in Group 2, 171 participants (98.8%) received Nimenrix and 1 participant received the MenACYW conjugate vaccine, and in Group 3, 116 participants (99.1%) received the MenACYW conjugate vaccine concomitantly with 9vHPV and Tdap-IPV vaccines.

At Visit 2, in Group 1, 168 participants (97.1%) received 9vHPV and Tdap-IPV vaccines group and in Group 2, 169 participants (97.7%) received 9vHPV vaccine and 168 participants (97.1%) received Tdap-IPV vaccine. One participant in Group 2 did not receive Tdap-IPV vaccine due to previous vaccination against tetanus, diphtheria, and pertussis.

Overall SafAS for any dose

SafAS contains participants who received at least one dose of study vaccines and have any safety data available (see table below).

Table 20: Safety overview after any injection – Overall Safety Analysis Set for any dose

	Group 1 (N=171)			Group 2 (N=171)			Group 3 (N=116)		
Period/ Participants experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Within 30 minutes after any vaccine injections									
Immediate unsolicited AE	0/171	0	(0 ; 2.1)	0/171	0	(0 ; 2.1)	0/116	0	(0 ; 3.1)
Immediate unsolicited AR	0/171	0	(0 ; 2.1)	0/171	0	(0 ; 2.1)	0/116	0	(0 ; 3.1)
Solicited reaction within solicited period after any vaccine injections	153/169	90.5	(85.1 ; 94.5)	151/170	88.8	(83.1 ; 93.1)	111/116	95.7	(90.2 ; 98.6)
Solicited injection site reaction	149/169	88.2	(82.3 ; 92.6)	141/170	82.9	(76.4 ; 88.3)	108/116	93.1	(86.9 ; 97.0)
Solicited injection site reaction after injection of MenACYW	97/169	57.4	(49.6 ; 65.0)	-	-	-	72/116	62.1	(52.6 ; 70.9)
Solicited injection site reaction after injection of Nimenrix	-	-	-	90/170	52.9	(45.1 ; 60.6)	-	-	-
Solicited injection site reaction after injection of 9vHPV	113/168	67.3	(59.6 ; 74.3)	125/165	75.8	(68.5 ; 82.1)	98/116	84.5	(76.6 ; 90.5)
Solicited injection site reaction after injection of Tdap-IPV	118/168	70.2	(62.7 ; 77.0)	117/164	71.3	(63.8 ; 78.1)	95/116	81.9	(73.7 ; 88.4)
Solicited systemic reaction	114/169	67.5	(59.8 ; 74.5)	112/170	65.9	(58.2 ; 73.0)	83/116	71.6	(62.4 ; 79.5)
Within 30 days after any vaccine injections									
Unsolicited AE	69/171	40.4	(32.9 ; 48.1)	49/171	28.7	(22.0 ; 36.1)	37/116	31.9	(23.6 ; 41.2)
Unsolicited AR	19/171	11.1	(6.8 ; 16.8)	12/171	7.0	(3.7 ; 11.9)	12/116	10.3	(5.5 ; 17.4)
Unsolicited injection site AR	13/171	7.6	(4.1 ; 12.6)	11/171	6.4	(3.3 ; 11.2)	11/116	9.5	(4.8 ; 16.3)
Unsolicited injection site AR after MenACYW	11/171	6.4	(3.3 ; 11.2)	-	-	-	4/116	3.4	(0.9 ; 8.6)
Unsolicited injection site AR after Nimenrix	-	-	-	4/171	2.3	(0.6 ; 5.9)	-	-	-
Unsolicited injection site AR after 9vHPV	3/171	1.8	(0.4 ; 5.0)	3/171	1.8	(0.4 ; 5.0)	5/116	4.3	(1.4 ; 9.8)
Unsolicited injection site AR after Tdap-IPV	1/171	0.6	(0 ; 3.2)	6/171	3.5	(1.3 ; 7.5)	4/116	3.4	(0.9 ; 8.6)
AE leading to study discontinuation	0/171	0	(0 ; 2.1)	0/171	0	(0 ; 2.1)	0/116	0	(0 ; 3.1)
SAE within 30 days after any vaccine injections	0/171	0	(0 ; 2.1)	0/171	0	(0 ; 2.1)	0/116	0	(0 ; 3.1)
Death	0/171	0	(0 ; 2.1)	0/171	0	(0 ; 2.1)	0/116	0	(0 ; 3.1)
AESI	0/171	0	(0 ; 2.1)	0/171	0	(0 ; 2.1)	0/116	0	(0 ; 3.1)
SAE throughout the study	0/171	0	(0 ; 2.1)	1/171	0.6	(0 ; 3.2)	0/116	0	(0 ; 3.1)
Death	0/171	0	(0 ; 2.1)	0/171	0	(0 ; 2.1)	0/116	0	(0 ; 3.1)
AESI	0/171	0	(0 ; 2.1)	0/171	0	(0 ; 2.1)	0/116	0	(0 ; 3.1)

Group 1: MenACYW conjugate vaccine on D01 and 9vHPV + Tdap-IPV vaccines on D31.
Group 2: Nimenrix on D01 and 9vHPV + Tdap-IPV vaccines on D31.
Group 3: MenACYW conjugate vaccine + 9vHPV + Tdap-IPV vaccines on D01.
n: number of participants experiencing the endpoint listed in the first column
M: number of participants with available data for the relevant endpoint
AR: Reactions related to the study vaccine
Study: MEQ00071 Program: T08025.sas Datasets=ADSL ADAE ADRC Output: PRODOPS/PLC16012/MEQ00071/CSR_01/REPORT/OUTPUT/T08025_i.rtf (31MAR2023 14:45)

Table 21: Safety overview after any injections - Participants from Overall Safety Analysis Set not impacted by the unblinding issue

Participants experiencing at least one:	Group 1 (N=99) n/M	%	(95% CI)	Group 2 (N=100) n/M	%	(95% CI)	Group 3 (N=116) n/M	%	(95% CI)
Within 30 minutes after any vaccine injections									
Immediate unsolicited AE	0/99	0	(0 ; 3.7)	0/100	0	(0 ; 3.6)	0/116	0	(0 ; 3.1)
Immediate unsolicited AR	0/99	0	(0 ; 3.7)	0/100	0	(0 ; 3.6)	0/116	0	(0 ; 3.1)
Solicited reaction within solicited period after any vaccine injections	88/97	90.7	(83.1 ; 95.7)	91/99	91.9	(84.7 ; 96.4)	111/116	95.7	(90.2 ; 98.6)
Solicited injection site reaction	85/97	87.6	(79.4 ; 93.4)	85/99	85.9	(77.4 ; 92.0)	108/116	93.1	(86.9 ; 97.0)
Solicited injection site reaction after injection of MenACYW	49/97	50.5	(40.2 ; 60.8)	-	-	-	72/116	62.1	(52.6 ; 70.9)
Solicited injection site reaction after injection of Nimenrix	-	-	-	50/99	50.5	(40.3 ; 60.7)	-	-	-
Solicited injection site reaction after injection of 9vHPV	66/97	68.0	(57.8 ; 77.1)	79/98	80.6	(71.4 ; 87.9)	98/116	84.5	(76.6 ; 90.5)
Solicited injection site reaction after injection of Tdap-IPV	68/97	70.1	(60.0 ; 79.0)	72/98	73.5	(63.6 ; 81.9)	95/116	81.9	(73.7 ; 88.4)
Solicited systemic reaction	61/97	62.9	(52.5 ; 72.5)	68/99	68.7	(58.6 ; 77.6)	83/116	71.6	(62.4 ; 79.5)
Within 30 days after any vaccine injections									
Unsolicited AE	35/99	35.4	(26.0 ; 45.6)	23/100	23.0	(15.2 ; 32.5)	37/116	31.9	(23.6 ; 41.2)
Unsolicited AR	4/99	4.0	(1.1 ; 10.0)	4/100	4.0	(1.1 ; 9.9)	12/116	10.3	(5.5 ; 17.4)
Unsolicited injection site AR	2/99	2.0	(0.2 ; 7.1)	4/100	4.0	(1.1 ; 9.9)	11/116	9.5	(4.8 ; 16.3)
Unsolicited injection site AR after MenACYW	2/99	2.0	(0.2 ; 7.1)	-	-	-	4/116	3.4	(0.9 ; 8.6)
Unsolicited injection site AR after Nimenrix	-	-	-	1/100	1.0	(0 ; 5.4)	-	-	-
Unsolicited injection site AR after 9vHPV	0/99	0	(0 ; 3.7)	1/100	1.0	(0 ; 5.4)	5/116	4.3	(1.4 ; 9.8)
Unsolicited injection site AR after Tdap-IPV	0/99	0	(0 ; 3.7)	2/100	2.0	(0.2 ; 7.0)	4/116	3.4	(0.9 ; 8.6)
AE leading to study discontinuation	0/99	0	(0 ; 3.7)	0/100	0	(0 ; 3.6)	0/116	0	(0 ; 3.1)
SAE within 30 days after any vaccine injections	0/99	0	(0 ; 3.7)	0/100	0	(0 ; 3.6)	0/116	0	(0 ; 3.1)
Death	0/99	0	(0 ; 3.7)	0/100	0	(0 ; 3.6)	0/116	0	(0 ; 3.1)
AESI	0/99	0	(0 ; 3.7)	0/100	0	(0 ; 3.6)	0/116	0	(0 ; 3.1)
SAE throughout the study	0/99	0	(0 ; 3.7)	1/100	1.0	(0 ; 5.4)	0/116	0	(0 ; 3.1)
Death	0/99	0	(0 ; 3.7)	0/100	0	(0 ; 3.6)	0/116	0	(0 ; 3.1)
AESI	0/99	0	(0 ; 3.7)	0/100	0	(0 ; 3.6)	0/116	0	(0 ; 3.1)

Group 1: MenACYW conjugate vaccine on D01 and 9vHPV + Tdap-IPV vaccines on D31.
Group 2: Nimenrix on D01 and 9vHPV + Tdap-IPV vaccines on D31.
Group 3: MenACYW conjugate vaccine + 9vHPV + Tdap-IPV vaccines on D01.
n: number of participants experiencing the endpoint listed in the first column
M: number of participants with available data for the relevant endpoint
AR: Reactions related to the study vaccine

Table 22: Safety overview after any injections - Participants from Overall Safety Analysis Set not impacted by the administration deviation

Participants experiencing at least one:	Group 1 (N=148) n/M	%	(95% CI)	Group 2 (N=147) n/M	%	(95% CI)	Group 3 (N=115) n/M	%	(95% CI)
Within 30 minutes after any vaccine injections									
Immediate unsolicited AE	0/148	0	(0 ; 2.5)	0/147	0	(0 ; 2.5)	0/115	0	(0 ; 3.2)
Immediate unsolicited AR	0/148	0	(0 ; 2.5)	0/147	0	(0 ; 2.5)	0/115	0	(0 ; 3.2)
Solicited reaction within solicited period after any vaccine injections	132/146	90.4	(84.4 ; 94.7)	128/146	87.7	(81.2 ; 92.5)	110/115	95.7	(90.1 ; 98.6)
Solicited injection site reaction	129/146	88.4	(82.0 ; 93.1)	120/146	82.2	(75.0 ; 88.0)	107/115	93.0	(86.8 ; 96.9)
Solicited injection site reaction after injection of MenACYW	88/146	60.3	(51.9 ; 68.3)	-	-	-	72/115	62.6	(53.1 ; 71.5)
Solicited injection site reaction after injection of Nimenrix	-	-	-	77/146	52.7	(44.3 ; 61.1)	-	-	-
Solicited injection site reaction after injection of 9vHPV	99/145	68.3	(60.0 ; 75.7)	106/142	74.6	(66.7 ; 81.6)	97/115	84.3	(76.4 ; 90.5)
Solicited injection site reaction after injection of Tdap-IPV	102/145	70.3	(62.2 ; 77.6)	100/141	70.9	(62.7 ; 78.3)	94/115	81.7	(73.5 ; 88.3)
Solicited systemic reaction	97/146	66.4	(58.2 ; 74.0)	93/146	63.7	(55.3 ; 71.5)	82/115	71.3	(62.1 ; 79.4)
Within 30 days after any vaccine injections									
Unsolicited AE	64/148	43.2	(35.1 ; 51.6)	45/147	30.6	(23.3 ; 38.7)	37/115	32.2	(23.8 ; 41.5)
Unsolicited AR	18/148	12.2	(7.4 ; 18.5)	12/147	8.2	(4.3 ; 13.8)	12/115	10.4	(5.5 ; 17.5)
Unsolicited injection site AR	13/148	8.8	(4.8 ; 14.6)	11/147	7.5	(3.8 ; 13.0)	11/115	9.6	(4.9 ; 16.5)
Unsolicited injection site AR after MenACYW	11/148	7.4	(3.8 ; 12.9)	-	-	-	4/115	3.5	(1.0 ; 8.7)
Unsolicited injection site AR after Nimenrix	-	-	-	4/147	2.7	(0.7 ; 6.8)	-	-	-
Unsolicited injection site AR after 9vHPV	3/148	2.0	(0.4 ; 5.8)	3/147	2.0	(0.4 ; 5.8)	5/115	4.3	(1.4 ; 9.9)
Unsolicited injection site AR after Tdap-IPV	1/148	0.7	(0 ; 3.7)	6/147	4.1	(1.5 ; 8.7)	4/115	3.5	(1.0 ; 8.7)
AE leading to study discontinuation	0/148	0	(0 ; 2.5)	0/147	0	(0 ; 2.5)	0/115	0	(0 ; 3.2)
SAE within 30 days after any vaccine injections	0/148	0	(0 ; 2.5)	0/147	0	(0 ; 2.5)	0/115	0	(0 ; 3.2)
Death	0/148	0	(0 ; 2.5)	0/147	0	(0 ; 2.5)	0/115	0	(0 ; 3.2)
AESI	0/148	0	(0 ; 2.5)	0/147	0	(0 ; 2.5)	0/115	0	(0 ; 3.2)
SAE throughout the study	0/148	0	(0 ; 2.5)	1/147	0.7	(0 ; 3.7)	0/115	0	(0 ; 3.2)
Death	0/148	0	(0 ; 2.5)	0/147	0	(0 ; 2.5)	0/115	0	(0 ; 3.2)
AESI	0/148	0	(0 ; 2.5)	0/147	0	(0 ; 2.5)	0/115	0	(0 ; 3.2)

Table 23: Summary of solicited reactions within 7 days after any vaccine injections - Overall Safety Analysis Set for any dose

	Group 1 (N=171)			Group 2 (N=171)			Group 3 (N=116)		
Participants experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Solicited reaction	153/169	90.5	(85.1 ; 94.5)	151/170	88.8	(83.1 ; 93.1)	111/116	95.7	(90.2 ; 98.6)
Grade 3 solicited reaction	32/169	18.9	(13.3 ; 25.7)	26/170	15.3	(10.2 ; 21.6)	30/116	25.9	(18.2 ; 34.8)
Solicited injection site reaction	149/169	88.2	(82.3 ; 92.6)	141/170	82.9	(76.4 ; 88.3)	108/116	93.1	(86.9 ; 97.0)
MenACYW	97/169	57.4	(49.6 ; 65.0)	-	-	-	72/116	62.1	(52.6 ; 70.9)
Nimenrix	-	-	-	90/170	52.9	(45.1 ; 60.6)	-	-	-
9vHPV	113/168	67.3	(59.6 ; 74.3)	125/165	75.8	(68.5 ; 82.1)	98/116	84.5	(76.6 ; 90.5)
Tdap-IPV	118/168	70.2	(62.7 ; 77.0)	117/164	71.3	(63.8 ; 78.1)	95/116	81.9	(73.7 ; 88.4)
Grade 3 injection site reaction	24/169	14.2	(9.3 ; 20.4)	19/170	11.2	(6.9 ; 16.9)	19/116	16.4	(10.2 ; 24.4)
MenACYW	7/169	4.1	(1.7 ; 8.3)	-	-	-	5/116	4.3	(1.4 ; 9.8)
Nimenrix	-	-	-	4/170	2.4	(0.6 ; 5.9)	-	-	-
9vHPV	13/168	7.7	(4.2 ; 12.9)	16/165	9.7	(5.6 ; 15.3)	15/116	12.9	(7.4 ; 20.4)
Tdap-IPV	13/168	7.7	(4.2 ; 12.9)	13/164	7.9	(4.3 ; 13.2)	15/116	12.9	(7.4 ; 20.4)
Solicited systemic reaction	114/169	67.5	(59.8 ; 74.5)	112/170	65.9	(58.2 ; 73.0)	83/116	71.6	(62.4 ; 79.5)
Grade 3 systemic reaction	19/169	11.2	(6.9 ; 17.0)	19/170	11.2	(6.9 ; 16.9)	22/116	19.0	(12.3 ; 27.3)

Group 1: MenACYW conjugate vaccine on D01 and 9vHPV + Tdap-IPV vaccines on D31
Group 2: Nimenrix on D01 and 9vHPV + Tdap-IPV vaccines on D31
Group 3: MenACYW conjugate vaccine + 9vHPV + Tdap-IPV vaccines on D01
n: number of participants experiencing the endpoint listed in the first column
M: number of participants with available data for the relevant endpoint

Table 24: Solicited injection site reactions after any vaccine injection, by maximum intensity during the solicited period - Overall Safety Analysis Set for any dose

		Group 1 (N=171)			Group 2 (N=171)			Group 3 (N=116)		
Participants experiencing at least one:	**Maximum intensity:**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
MenACYW										
Injection site Pain	Any	91/169	53.8	(46.0 ; 61.5)	-	-	-	69/116	59.5	(50.0 ; 68.5)
	Grade 1	60/169	35.5	(28.3 ; 43.2)	-	-	-	44/116	37.9	(29.1 ; 47.4)
	Grade 2	27/169	16.0	(10.8 ; 22.4)	-	-	-	23/116	19.8	(13.0 ; 28.3)
	Grade 3	4/169	2.4	(0.6 ; 5.9)	-	-	-	2/116	1.7	(0.2 ; 6.1)
Injection site Erythema	Any	19/169	11.2	(6.9 ; 17.0)	-	-	-	11/116	9.5	(4.8 ; 16.3)
	Grade 1	5/169	3.0	(1.0 ; 6.8)	-	-	-	3/116	2.6	(0.5 ; 7.4)
	Grade 2	10/169	5.9	(2.9 ; 10.6)	-	-	-	5/116	4.3	(1.4 ; 9.8)
	Grade 3	4/169	2.4	(0.6 ; 5.9)	-	-	-	3/116	2.6	(0.5 ; 7.4)
Injection site Swelling	Any	17/169	10.1	(6.0 ; 15.6)	-	-	-	12/116	10.3	(5.5 ; 17.4)
	Grade 1	8/169	4.7	(2.1 ; 9.1)	-	-	-	5/116	4.3	(1.4 ; 9.8)
	Grade 2	9/169	5.3	(2.5 ; 9.9)	-	-	-	6/116	5.2	(1.9 ; 10.9)
	Grade 3	0/169	0	(0 ; 2.2)	-	-	-	1/116	0.9	(0 ; 4.7)
Nimenrix										
Injection site Pain	Any	-	-	-	87/170	51.2	(43.4 ; 58.9)	-	-	-
	Grade 1	-	-	-	60/170	35.3	(28.1 ; 43.0)	-	-	-
	Grade 2	-	-	-	23/170	13.5	(8.8 ; 19.6)	-	-	-
	Grade 3	-	-	-	4/170	2.4	(0.6 ; 5.9)	-	-	-
Injection site Erythema	Any	-	-	-	3/170	1.8	(0.4 ; 5.1)	-	-	-
	Grade 1	-	-	-	1/170	0.6	(0 ; 3.2)	-	-	-
	Grade 2	-	-	-	2/170	1.2	(0.1 ; 4.2)	-	-	-
	Grade 3	-	-	-	0/170	0	(0 ; 2.1)	-	-	-
Injection site Swelling	Any	-	-	-	7/170	4.1	(1.7 ; 8.3)	-	-	-
	Grade 1	-	-	-	5/170	2.9	(1.0 ; 6.7)	-	-	-

		Group 1 (N=171)			Group 2 (N=171)			Group 3 (N=116)		
Participants experiencing at least one:	**Maximum intensity:**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
	Grade 2	-	-	-	2/170	1.2	(0.1 ; 4.2)	-	-	-
	Grade 3	-	-	-	0/170	0	(0 ; 2.1)	-	-	-
9vHPV										
Injection site Pain	Any	113/168	67.3	(59.6 ; 74.3)	125/165	75.8	(68.5 ; 82.1)	97/116	83.6	(75.6 ; 89.8)
	Grade 1	62/168	36.9	(29.6 ; 44.7)	68/165	41.2	(33.6 ; 49.1)	39/116	33.6	(25.1 ; 43.0)
	Grade 2	38/168	22.6	(16.5 ; 29.7)	41/165	24.8	(18.5 ; 32.2)	43/116	37.1	(28.3 ; 46.5)
	Grade 3	13/168	7.7	(4.2 ; 12.9)	16/165	9.7	(5.6 ; 15.3)	15/116	12.9	(7.4 ; 20.4)
Injection site Erythema	Any	7/168	4.2	(1.7 ; 8.4)	3/165	1.8	(0.4 ; 5.2)	6/116	5.2	(1.9 ; 10.9)
	Grade 1	6/168	3.6	(1.3 ; 7.6)	3/165	1.8	(0.4 ; 5.2)	4/116	3.4	(0.9 ; 8.6)
	Grade 2	1/168	0.6	(0 ; 3.3)	0/165	0	(0 ; 2.2)	2/116	1.7	(0.2 ; 6.1)
	Grade 3	0/168	0	(0 ; 2.2)	0/165	0	(0 ; 2.2)	0/116	0	(0 ; 3.1)
Injection site Swelling	Any	4/168	2.4	(0.7 ; 6.0)	3/165	1.8	(0.4 ; 5.2)	7/116	6.0	(2.5 ; 12.0)
	Grade 1	3/168	1.8	(0.4 ; 5.1)	3/165	1.8	(0.4 ; 5.2)	4/116	3.4	(0.9 ; 8.6)
	Grade 2	1/168	0.6	(0 ; 3.3)	0/165	0	(0 ; 2.2)	3/116	2.6	(0.5 ; 7.4)
	Grade 3	0/168	0	(0 ; 2.2)	0/165	0	(0 ; 2.2)	0/116	0	(0 ; 3.1)
Tdap-IPV										
Injection site Pain	Any	116/168	69.0	(61.5 ; 75.9)	117/164	71.3	(63.8 ; 78.1)	95/116	81.9	(73.7 ; 88.4)
	Grade 1	60/168	35.7	(28.5 ; 43.5)	65/164	39.6	(32.1 ; 47.6)	41/116	35.3	(26.7 ; 44.8)
	Grade 2	43/168	25.6	(19.2 ; 32.9)	39/164	23.8	(17.5 ; 31.0)	40/116	34.5	(25.9 ; 43.9)
	Grade 3	13/168	7.7	(4.2 ; 12.9)	13/164	7.9	(4.3 ; 13.2)	14/116	12.1	(6.8 ; 19.4)
Injection site Erythema	Any	9/168	5.4	(2.5 ; 9.9)	5/164	3.0	(1.0 ; 7.0)	13/116	11.2	(6.1 ; 18.4)
	Grade 1	7/168	4.2	(1.7 ; 8.4)	4/164	2.4	(0.7 ; 6.1)	8/116	6.9	(3.0 ; 13.1)
	Grade 2	2/168	1.2	(0.1 ; 4.2)	1/164	0.6	(0 ; 3.4)	4/116	3.4	(0.9 ; 8.6)
	Grade 3	0/168	0	(0 ; 2.2)	0/164	0	(0 ; 2.2)	1/116	0.9	(0 ; 4.7)
Injection site Swelling	Any	9/168	5.4	(2.5 ; 9.9)	3/164	1.8	(0.4 ; 5.3)	10/116	8.6	(4.2 ; 15.3)
	Grade 1	9/168	5.4	(2.5 ; 9.9)	3/164	1.8	(0.4 ; 5.3)	5/116	4.3	(1.4 ; 9.8)

	Grade 2	0/168	0	(0 ; 2.2)	0/164	0	(0 ; 2.2)	4/116	3.4	(0.9 ; 8.6)
	Grade 3	0/168	0	(0 ; 2.2)	0/164	0	(0 ; 2.2)	1/116	0.9	(0 ; 4.7)

Group 1: MenACYW conjugate vaccine on D01 and 9vHPV + Tdap-IPV vaccines on D31
Group 2: Nimenrix on D01 and 9vHPV + Tdap-IPV vaccines on D31
Group 3: MenACYW conjugate vaccine + 9vHPV + Tdap-IPV vaccines on D01
n: number of participants experiencing the endpoint listed in the first two columns
M: number of participants with available data for the relevant endpoint; N: number of participants that have received at least one dose of the vaccination

Table 25: Solicited systemic reactions after vaccine injection, by maximum intensity during the solicited period - Overall Safety Analysis Set for any dose

		Group 1 (N=171)			Group 2 (N=171)			Group 3 (N=116)		
Participants experiencing at least one:	**Maximum intensity:**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Fever	Any	12/169	7.1	(3.7 ; 12.1)	11/170	6.5	(3.3 ; 11.3)	6/116	5.2	(1.9 ; 10.9)
	Grade 1	7/169	4.1	(1.7 ; 8.3)	8/170	4.7	(2.1 ; 9.1)	4/116	3.4	(0.9 ; 8.6)
	Grade 2	2/169	1.2	(0.1 ; 4.2)	2/170	1.2	(0.1 ; 4.2)	2/116	1.7	(0.2 ; 6.1)
	Grade 3	3/169	1.8	(0.4 ; 5.1)	1/170	0.6	(0 ; 3.2)	0/116	0	(0 ; 3.1)
Headache	Any	75/169	44.4	(36.8 ; 52.2)	64/170	37.6	(30.3 ; 45.4)	52/116	44.8	(35.6 ; 54.3)
	Grade 1	38/169	22.5	(16.4 ; 29.5)	35/170	20.6	(14.8 ; 27.5)	24/116	20.7	(13.7 ; 29.2)
	Grade 2	29/169	17.2	(11.8 ; 23.7)	18/170	10.6	(6.4 ; 16.2)	16/116	13.8	(8.1 ; 21.4)
	Grade 3	8/169	4.7	(2.1 ; 9.1)	11/170	6.5	(3.3 ; 11.3)	12/116	10.3	(5.5 ; 17.4)
Malaise	Any	65/169	38.5	(31.1 ; 46.2)	48/170	28.2	(21.6 ; 35.6)	42/116	36.2	(27.5 ; 45.6)
	Grade 1	33/169	19.5	(13.8 ; 26.3)	26/170	15.3	(10.2 ; 21.6)	12/116	10.3	(5.5 ; 17.4)
	Grade 2	24/169	14.2	(9.3 ; 20.4)	13/170	7.6	(4.1 ; 12.7)	19/116	16.4	(10.2 ; 24.4)
	Grade 3	8/169	4.7	(2.1 ; 9.1)	9/170	5.3	(2.4 ; 9.8)	11/116	9.5	(4.8 ; 16.3)
Myalgia	Any	84/169	49.7	(41.9 ; 57.5)	81/170	47.6	(39.9 ; 55.4)	67/116	57.8	(48.2 ; 66.9)
	Grade 1	42/169	24.9	(18.5 ; 32.1)	39/170	22.9	(16.9 ; 30.0)	27/116	23.3	(15.9 ; 32.0)
	Grade 2	30/169	17.8	(12.3 ; 24.4)	29/170	17.1	(11.7 ; 23.6)	29/116	25.0	(17.4 ; 33.9)
	Grade 3	12/169	7.1	(3.7 ; 12.1)	13/170	7.6	(4.1 ; 12.7)	11/116	9.5	(4.8 ; 16.3)

Unsolicited AEs after any vaccination within 30 days of vaccination

Table 26: Summary of unsolicited AEs within 30 days (from D1 to D31) after any vaccine injections - Overall Safety Analysis Set for any dose

	Group 1 (N=171)				Group 2 (N=171)				Group 3 (N=116)			
Participants experiencing at least one:	**n**	**%**	**(95% CI)**	**n AEs**	**n**	**%**	**(95% CI)**	**n AEs**	**n**	**%**	**(95% CI)**	**n AEs**
Immediate unsolicited AE	0	0	(0 ; 2.1)	0	0	0	(0 ; 2.1)	0	0	0	(0 ; 3.1)	0
Grade 3 immediate unsolicited AE	0	0	(0 ; 2.1)	0	0	0	(0 ; 2.1)	0	0	0	(0 ; 3.1)	0
Immediate unsolicited AR	0	0	(0 ; 2.1)	0	0	0	(0 ; 2.1)	0	0	0	(0 ; 3.1)	0
Grade 3 immediate unsolicited AR	0	0	(0 ; 2.1)	0	0	0	(0 ; 2.1)	0	0	0	(0 ; 3.1)	0
Unsolicited AE	69	40.4	(32.9 ; 48.1)	113	49	28.7	(22.0 ; 36.1)	81	37	31.9	(23.6 ; 41.2)	62
Grade 3 unsolicited AE	4	2.3	(0.6 ; 5.9)	5	1	0.6	(0 ; 3.2)	1	3	2.6	(0.5 ; 7.4)	3
Unsolicited AR	19	11.1	(6.8 ; 16.8)	26	12	7.0	(3.7 ; 11.9)	16	12	10.3	(5.5 ; 17.4)	22
Grade 3 unsolicited AR	1	0.6	(0 ; 3.2)	1	0	0	(0 ; 2.1)	0	1	0.9	(0 ; 4.7)	1
Unsolicited injection site AR	13	7.6	(4.1 ; 12.6)	15	11	6.4	(3.3 ; 11.2)	13	11	9.5	(4.8 ; 16.3)	20
After injection of MenACYW	11	6.4	(3.3 ; 11.2)	11	-	-	-	-	4	3.4	(0.9 ; 8.6)	6
After injection of Nimenrix	-	-	-	-	4	2.3	(0.6 ; 5.9)	4	-	-	-	-
After injection of 9vHPV	3	1.8	(0.4 ; 5.0)	3	3	1.8	(0.4 ; 5.0)	3	5	4.3	(1.4 ; 9.8)	6
After injection of Tdap-IPV	1	0.6	(0 ; 3.2)	1	6	3.5	(1.3 ; 7.5)	6	4	3.4	(0.9 ; 8.6)	8
Grade 3 unsolicited injection site AR	1	0.6	(0 ; 3.2)	1	0	0	(0 ; 2.1)	0	1	0.9	(0 ; 4.7)	1
After injection of MenACYW	1	0.6	(0 ; 3.2)	1	-	-	-	-	1	0.9	(0 ; 4.7)	1
After injection of Nimenrix	-	-	-	-	0	0	(0 ; 2.1)	0	-	-	-	-
After injection of 9vHPV	0	0	(0 ; 2.1)	0	0	0	(0 ; 2.1)	0	0	0	(0 ; 3.1)	0
After injection of Tdap-IPV	0	0	(0 ; 2.1)	0	0	0	(0 ; 2.1)	0	0	0	(0 ; 3.1)	0
Unsolicited systemic AE	62	36.3	(29.1 ; 43.9)	98	44	25.7	(19.4 ; 33.0)	68	31	26.7	(18.9 ; 35.7)	42
Grade 3 unsolicited systemic AE	3	1.8	(0.4 ; 5.0)	4	1	0.6	(0 ; 3.2)	1	2	1.7	(0.2 ; 6.1)	2
Unsolicited systemic AR	6	3.5	(1.3 ; 7.5)	11	3	1.8	(0.4 ; 5.0)	3	2	1.7	(0.2 ; 6.1)	2
Grade 3 unsolicited systemic AR	0	0	(0 ; 2.1)	0	0	0	(0 ; 2.1)	0	0	0	(0 ; 3.1)	0
SAE	0	0	(0 ; 2.1)	0	0	0	(0 ; 2.1)	0	0	0	(0 ; 3.1)	0
Grade 3 SAE	0	0	(0 ; 2.1)	0	0	0	(0 ; 2.1)	0	0	0	(0 ; 3.1)	0

Group 1: MenACYW conjugate vaccine on D01 and 9vHPV + Tdap-IPV vaccines on D31. Group 2: Nimenrix on D01 and 9vHPV + Tdap-IPV vaccines on D31.
Group 3: MenACYW conjugate vaccine + 9vHPV + Tdap-IPV vaccines on D01.
n: number of participants experiencing the endpoint listed in the first column
n AEs: number of AEs
AR: Reactions related to the study vaccine
Immediate unsolicited AE' is collected only for immediate unsolicited systemic AE.
Unsolicited AE' also includes immediate and serious unsolicited AEs.

Unsolicited AEs within 30 days of vaccination were mainly reported in the following SOCs: “Infections and infestations” (21.6% [37/171]) and “General disorders and administration site conditions” (11.7% [20/171]) in Group 1; “Infections and infestations” (10.5% [18/171]), “General disorders and administration site conditions” (7.0% [12/171]), and “Injury, poisoning and procedural complications” (5.8% [10/171]) in Group 2; and “Infections and infestations” (12.1% [14/116]), “General disorders and administration site conditions” (9.5% [11/116]), and “Gastrointestinal disorders” (7.8% [9/116]) in Group 3. Most unsolicited AEs started during the time period D1-D4 and resolved after 1-3 days and 4-7 days in Group 1 and in Group 3. Most unsolicited AEs started during the time period D1-D4 and resolved after 1-3 days in Group 2. At least 1 Grade 3 unsolicited AE was reported in 2.3% (4/171) of participants in Group 1, 0.6% (1/171) of participants in Group 2, and 2.6% (3/116) of participants in Group 3.

Unsolicited ARs after any vaccination within 30 days of vaccination

At least 1 unsolicited AE was assessed as related to the vaccine by the Investigator in 11.1% (19/171) of participants in Group 1, 7.0% (12/171) of participants in Group 2, and 10.3% (12/116) of participants in Group 3. The main unsolicited injection site ARs reported after vaccination in the SOC “General disorders and administration site conditions” were: in Group 1, bruising (4.1% [7/171]), pruritus (1.8% [3/171]) and haematoma (1.2% [2/171]); in Group 2, bruising (5.3% [9/171]); and in Group 3, bruising (2.6% [3/116]), haematoma (2.6% [3/116]) and pruritus (2.6% [3/116]).

At least 1 unsolicited systemic AR was reported in 3.5% (6/171) of participants in Group 1, 1.8% (3/171) of participants in Group 2, and 1.7% (2/116) of participants in Group 3 within 30 days of vaccination. Unsolicited systemic ARs within 30 days of vaccination were mainly reported in the following SOCs: “Gastrointestinal disorders” (1.2% [2/171]), “Blood and lymphatic system disorders” (0.6% [1/171]), “Eye disorders” (0.6% [1/171]), “Infections and infestations” (0.6% [1/171]), and “Psychiatric disorders” (0.6% [1/171]) in Group 1; “Gastrointestinal disorders” (0.6% [1/171]), “Nervous system disorders” (0.6% [1/171]), and “Metabolism and nutrition disorders” (0.6% [1/171]) in Group 2; and “Gastrointestinal disorders” (0.9% [1/116]) and “Nervous system disorders” (0.9% [1/116]) in Group 3. No participants reported any Grade 3 unsolicited systemic ARs within 30 days of vaccination in any group.

SafAS for vaccination at Visit 1 (SafAS1)

SafAS1 contains participants who received at least one dose of study vaccines at Visit 1 (all groups) and have safety data available. On D01, participants were scheduled to receive MenQuadfi (Group 1), Nimenrix (Group 2), or MenQuadfi + 9vHPV + Tdap-IPV vaccines (Group 3).

Table 27: Summary of solicited reactions within 7 days after vaccine injection at Visit 1 - Safety Analysis Set for vaccination at Visit 1

	Group 1 (N=171)			Group 2 (N=171)			Group 3 (N=116)		
Participants experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Solicited reaction	116/169	68.6	(61.1 ; 75.5)	111/170	65.3	(57.6 ; 72.4)	111/116	95.7	(90.2 ; 98.6)
Grade 3 solicited reaction	14/169	8.3	(4.6 ; 13.5)	14/170	8.2	(4.6 ; 13.4)	30/116	25.9	(18.2 ; 34.8)
Solicited injection site reaction	97/169	57.4	(49.6 ; 65.0)	90/170	52.9	(45.1 ; 60.6)	108/116	93.1	(86.9 ; 97.0)
MenACYW	97/169	57.4	(49.6 ; 65.0)	-	-	-	72/116	62.1	(52.6 ; 70.9)
Nimenrix	-	-	-	90/170	52.9	(45.1 ; 60.6)	-	-	-
9vHPV	-	-	-	-	-	-	98/116	84.5	(76.6 ; 90.5)
Tdap-IPV	-	-	-	-	-	-	95/116	81.9	(73.7 ; 88.4)
Grade 3 injection site reaction	7/169	4.1	(1.7 ; 8.3)	4/170	2.4	(0.6 ; 5.9)	19/116	16.4	(10.2 ; 24.4)
MenACYW	7/169	4.1	(1.7 ; 8.3)	-	-	-	5/116	4.3	(1.4 ; 9.8)
Nimenrix	-	-	-	4/170	2.4	(0.6 ; 5.9)	-	-	-
9vHPV	-	-	-	-	-	-	15/116	12.9	(7.4 ; 20.4)
Tdap-IPV	-	-	-	-	-	-	15/116	12.9	(7.4 ; 20.4)
Solicited systemic reaction	86/169	50.9	(43.1 ; 58.6)	78/170	45.9	(38.2 ; 53.7)	83/116	71.6	(62.4 ; 79.5)
Grade 3 systemic reaction	10/169	5.9	(2.9 ; 10.6)	12/170	7.1	(3.7 ; 12.0)	22/116	19.0	(12.3 ; 27.3)

Table 28: Solicited injection site reactions after vaccine injection at Visit 1, by maximum intensity during the solicited period - SafAS1

		Group 1 (N=171)			Group 2 (N=171)			Group 3 (N=116)		
Participants experiencing at least one:	**Maximum intensity:**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
MenACYW										
Injection site Pain	Any	91/169	53.8	(46.0 ; 61.5)	-	-	-	69/116	59.5	(50.0 ; 68.5)
	Grade 1	60/169	35.5	(28.3 ; 43.2)	-	-	-	44/116	37.9	(29.1 ; 47.4)
	Grade 2	27/169	16.0	(10.8 ; 22.4)	-	-	-	23/116	19.8	(13.0 ; 28.3)
	Grade 3	4/169	2.4	(0.6 ; 5.9)	-	-	-	2/116	1.7	(0.2 ; 6.1)
Injection site Erythema	Any	19/169	11.2	(6.9 ; 17.0)	-	-	-	11/116	9.5	(4.8 ; 16.3)
	Grade 1	5/169	3.0	(1.0 ; 6.8)	-	-	-	3/116	2.6	(0.5 ; 7.4)
	Grade 2	10/169	5.9	(2.9 ; 10.6)	-	-	-	5/116	4.3	(1.4 ; 9.8)
	Grade 3	4/169	2.4	(0.6 ; 5.9)	-	-	-	3/116	2.6	(0.5 ; 7.4)
Injection site Swelling	Any	17/169	10.1	(6.0 ; 15.6)	-	-	-	12/116	10.3	(5.5 ; 17.4)
	Grade 1	8/169	4.7	(2.1 ; 9.1)	-	-	-	5/116	4.3	(1.4 ; 9.8)
	Grade 2	9/169	5.3	(2.5 ; 9.9)	-	-	-	6/116	5.2	(1.9 ; 10.9)
	Grade 3	0/169	0	(0 ; 2.2)	-	-	-	1/116	0.9	(0 ; 4.7)
Nimenrix										
Injection site Pain	Any	-	-	-	87/170	51.2	(43.4 ; 58.9)	-	-	-
	Grade 1	-	-	-	60/170	35.3	(28.1 ; 43.0)	-	-	-
	Grade 2	-	-	-	23/170	13.5	(8.8 ; 19.6)	-	-	-
	Grade 3	-	-	-	4/170	2.4	(0.6 ; 5.9)	-	-	-
Injection site Erythema	Any	-	-	-	3/170	1.8	(0.4 ; 5.1)	-	-	-
	Grade 1	-	-	-	1/170	0.6	(0 ; 3.2)	-	-	-
	Grade 2	-	-	-	2/170	1.2	(0.1 ; 4.2)	-	-	-
	Grade 3	-	-	-	0/170	0	(0 ; 2.1)	-	-	-
Injection site Swelling	Any	-	-	-	7/170	4.1	(1.7 ; 8.3)	-	-	-
	Grade 1	-	-	-	5/170	2.9	(1.0 ; 6.7)	-	-	-
	Grade 2	-	-	-	2/170	1.2	(0.1 ; 4.2)	-	-	-
	Grade 3	-	-	-	0/170	0	(0 ; 2.1)	-	-	-
9vHPV										
Injection site Pain	Any	-	-	-	-	-	-	97/116	83.6	(75.6 ; 89.8)
	Grade 1	-	-	-	-	-	-	39/116	33.6	(25.1 ; 43.0)
	Grade 2	-	-	-	-	-	-	43/116	37.1	(28.3 ; 46.5)
	Grade 3	-	-	-	-	-	-	15/116	12.9	(7.4 ; 20.4)
Injection site Erythema	Any	-	-	-	-	-	-	6/116	5.2	(1.9 ; 10.9)
	Grade 1	-	-	-	-	-	-	4/116	3.4	(0.9 ; 8.6)
	Grade 2	-	-	-	-	-	-	2/116	1.7	(0.2 ; 6.1)
	Grade 3	-	-	-	-	-	-	0/116	0	(0 ; 3.1)
Injection site Swelling	Any	-	-	-	-	-	-	7/116	6.0	(2.5 ; 12.0)
	Grade 1	-	-	-	-	-	-	4/116	3.4	(0.9 ; 8.6)
	Grade 2	-	-	-	-	-	-	3/116	2.6	(0.5 ; 7.4)
	Grade 3	-	-	-	-	-	-	0/116	0	(0 ; 3.1)
Tdap-IPV										
Injection site Pain	Any	-	-	-	-	-	-	95/116	81.9	(73.7 ; 88.4)
	Grade 1	-	-	-	-	-	-	41/116	35.3	(26.7 ; 44.8)
	Grade 2	-	-	-	-	-	-	40/116	34.5	(25.9 ; 43.9)
	Grade 3	-	-	-	-	-	-	14/116	12.1	(6.8 ; 19.4)
Injection site Erythema	Any	-	-	-	-	-	-	13/116	11.2	(6.1 ; 18.4)
	Grade 1	-	-	-	-	-	-	8/116	6.9	(3.0 ; 13.1)
	Grade 2	-	-	-	-	-	-	4/116	3.4	(0.9 ; 8.6)
	Grade 3	-	-	-	-	-	-	1/116	0.9	(0 ; 4.7)
Injection site Swelling	Any	-	-	-	-	-	-	10/116	8.6	(4.2 ; 15.3)
	Grade 1	-	-	-	-	-	-	5/116	4.3	(1.4 ; 9.8)
	Grade 2	-	-	-	-	-	-	4/116	3.4	(0.9 ; 8.6)
	Grade 3	-	-	-	-	-	-	1/116	0.9	(0 ; 4.7)

Table 29: Solicited systemic reactions after vaccine injection at Visit 1, by maximum intensity during the solicited period – SafAS1

Participants experiencing at least one:	Maximum intensity:	Group 1 (N=171) n/M	%	(95% CI)	Group 2 (N=171) n/M	%	(95% CI)	Group 3 (N=116) n/M	%	(95% CI)
Fever	Any	7/169	4.1	(1.7 ; 8.3)	4/170	2.4	(0.6 ; 5.9)	6/116	5.2	(1.9 ; 10.9)
	Grade 1	2/169	1.2	(0.1 ; 4.2)	3/170	1.8	(0.4 ; 5.1)	4/116	3.4	(0.9 ; 8.6)
	Grade 2	2/169	1.2	(0.1 ; 4.2)	1/170	0.6	(0 ; 3.2)	2/116	1.7	(0.2 ; 6.1)
	Grade 3	3/169	1.8	(0.4 ; 5.1)	0/170	0	(0 ; 2.1)	0/116	0	(0 ; 3.1)
Headache	Any	59/168	35.1	(27.9 ; 42.8)	44/170	25.9	(19.5 ; 33.1)	52/116	44.8	(35.6 ; 54.3)
	Grade 1	31/168	18.5	(12.9 ; 25.2)	27/170	15.9	(10.7 ; 22.3)	24/116	20.7	(13.7 ; 29.2)
	Grade 2	22/168	13.1	(8.4 ; 19.2)	8/170	4.7	(2.1 ; 9.1)	16/116	13.8	(8.1 ; 21.4)
	Grade 3	6/168	3.6	(1.3 ; 7.6)	9/170	5.3	(2.4 ; 9.8)	12/116	10.3	(5.5 ; 17.4)
Malaise	Any	46/169	27.2	(20.7 ; 34.6)	32/170	18.8	(13.2 ; 25.5)	42/116	36.2	(27.5 ; 45.6)
	Grade 1	23/169	13.6	(8.8 ; 19.7)	18/170	10.6	(6.4 ; 16.2)	12/116	10.3	(5.5 ; 17.4)
	Grade 2	17/169	10.1	(6.0 ; 15.6)	8/170	4.7	(2.1 ; 9.1)	19/116	16.4	(10.2 ; 24.4)
	Grade 3	6/169	3.6	(1.3 ; 7.6)	6/170	3.5	(1.3 ; 7.5)	11/116	9.5	(4.8 ; 16.3)
Myalgia	Any	51/169	30.2	(23.4 ; 37.7)	53/170	31.2	(24.3 ; 38.7)	67/116	57.8	(48.2 ; 66.9)
	Grade 1	28/169	16.6	(11.3 ; 23.0)	33/170	19.4	(13.8 ; 26.2)	27/116	23.3	(15.9 ; 32.0)
	Grade 2	18/169	10.7	(6.4 ; 16.3)	14/170	8.2	(4.6 ; 13.4)	29/116	25.0	(17.4 ; 33.9)
	Grade 3	5/169	3.0	(1.0 ; 6.8)	6/170	3.5	(1.3 ; 7.5)	11/116	9.5	(4.8 ; 16.3)

Unsolicited AEs in the SafAS1

Table 30: Summary of unsolicited AEs within 30 days (from D1 to D31) after any vaccine injections at Visit 1 - Safety Analysis Set for vaccination at Visit 1

Participants experiencing at least one:	Group 1 (N=171) n	%	(95% CI)	n AEs	Group 2 (N=171) n	%	(95% CI)	n AEs	Group 3 (N=116) n	%	(95% CI)	n AEs
Immediate unsolicited AE	0	0	(0 ; 2.1)	0	0	0	(0 ; 2.1)	0	0	0	(0 ; 3.1)	0
Grade 3 immediate unsolicited AE	0	0	(0 ; 2.1)	0	0	0	(0 ; 2.1)	0	0	0	(0 ; 3.1)	0
Immediate unsolicited AR	0	0	(0 ; 2.1)	0	0	0	(0 ; 2.1)	0	0	0	(0 ; 3.1)	0
Grade 3 immediate unsolicited AR	0	0	(0 ; 2.1)	0	0	0	(0 ; 2.1)	0	0	0	(0 ; 3.1)	0
Unsolicited AE	49	28.7	(22.0 ; 36.1)	71	31	18.1	(12.7 ; 24.7)	44	37	31.9	(23.6 ; 41.2)	62
Grade 3 unsolicited AE	3	1.8	(0.4 ; 5.0)	3	1	0.6	(0 ; 3.2)	1	3	2.6	(0.5 ; 7.4)	3
Unsolicited AR	15	8.8	(5.0 ; 14.1)	18	6	3.5	(1.3 ; 7.5)	6	12	10.3	(5.5 ; 17.4)	22
Grade 3 unsolicited AR	1	0.6	(0 ; 3.2)	1	0	0	(0 ; 2.1)	0	1	0.9	(0 ; 4.7)	1
Unsolicited injection site AR	11	6.4	(3.3 ; 11.2)	11	4	2.3	(0.6 ; 5.9)	4	11	9.5	(4.8 ; 16.3)	20
After injection of MenACYW	11	6.4	(3.3 ; 11.2)	11	-	-	-	-	4	3.4	(0.9 ; 8.6)	6
After injection of Nimenrix	-	-	-	-	4	2.3	(0.6 ; 5.9)	4	-	-	-	-
After injection of 9vHPV	0	0	(0 ; 2.1)	0	0	0	(0 ; 2.1)	0	5	4.3	(1.4 ; 9.8)	6
After injection of Tdap-IPV	0	0	(0 ; 2.1)	0	0	0	(0 ; 2.1)	0	4	3.4	(0.9 ; 8.6)	8
Grade 3 unsolicited injection site AR	1	0.6	(0 ; 3.2)	1	0	0	(0 ; 2.1)	0	1	0.9	(0 ; 4.7)	1
After injection of MenACYW	1	0.6	(0 ; 3.2)	1	-	-	-	-	1	0.9	(0 ; 4.7)	1
After injection of Nimenrix	-	-	-	-	0	0	(0 ; 2.1)	0	-	-	-	-
After injection of 9vHPV	0	0	(0 ; 2.1)	0	0	0	(0 ; 2.1)	0	0	0	(0 ; 3.1)	0
After injection of Tdap-IPV	0	0	(0 ; 2.1)	0	0	0	(0 ; 2.1)	0	0	0	(0 ; 3.1)	0
Unsolicited systemic AE	41	24.0	(17.8 ; 31.1)	60	28	16.4	(11.2 ; 22.8)	40	31	26.7	(18.9 ; 35.7)	42
Grade 3 unsolicited systemic AE	2	1.2	(0.1 ; 4.2)	2	1	0.6	(0 ; 3.2)	1	2	1.7	(0.2 ; 6.1)	2
Unsolicited systemic AR	4	2.3	(0.6 ; 5.9)	7	2	1.2	(0.1 ; 4.2)	2	2	1.7	(0.2 ; 6.1)	2
Grade 3 unsolicited systemic AR	0	0	(0 ; 2.1)	0	0	0	(0 ; 2.1)	0	0	0	(0 ; 3.1)	0
SAE	0	0	(0 ; 2.1)	0	0	0	(0 ; 2.1)	0	0	0	(0 ; 3.1)	0
Grade 3 SAE	0	0	(0 ; 2.1)	0	0	0	(0 ; 2.1)	0	0	0	(0 ; 3.1)	0

Group 1: MenACYW conjugate vaccine on D01 and 9vHPV + Tdap-IPV vaccines on D31. Group 2: Nimenrix on D01 and 9vHPV + Tdap-IPV vaccines on D31.
Group 3: MenACYW conjugate vaccine + 9vHPV + Tdap-IPV vaccines on D01.
n: number of participants experiencing the endpoint listed in the first column
n AEs: number of AEs
AR: Reactions related to the study vaccine
Immediate unsolicited AE' is collected only for immediate unsolicited systemic AE.
Unsolicited AE' also includes immediate and serious unsolicited AEs.

Unsolicited AEs within 30 days of vaccination were mainly reported in the following SOCs: “Infections and infestations” (11.7% [20/171]) and “General disorders and administration site conditions” (9.4% [16/171]) in Group 1; “Infections and infestations” (7.0% [12/171]) in Group 2; and “Infections and infestations” (12.1% [14/116]), “General disorders and administration site conditions” (9.5% [11/116]), and “Gastrointestinal disorders” (7.8% [9/116]) in Group 3. Most unsolicited AEs started during the time period D1-D4 and resolved after 1-3 days in Group 1 and in Group 2. Most unsolicited AEs started during the time period D1-D4 and resolved after 1-3 days and 4-7 days in Group 3. At

least 1 Grade 3 unsolicited AE was reported in 1.8% (3/171) of participants in Group 1, 0.6% (1/171) of participants in Group 2, and 2.6% (3/116) of participants in Group 3.

SafAS for vaccination at Visit 2 (SafAS2)

SafAS2 contains participants who received at least one dose of study vaccines at Visit 2 (Groups 1 and 2) and have safety data available.

Table 31: Summary of solicited reactions within 7 days after vaccine injection at Visit 2 - Safety Analysis Set for vaccination at Visit 2

	Group 1 (N=169)			Group 2 (N=168)		
Participants experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Solicited reaction	133/168	79.2	(72.2 ; 85.0)	136/165	82.4	(75.7 ; 87.9)
Grade 3 solicited reaction	20/168	11.9	(7.4 ; 17.8)	19/165	11.5	(7.1 ; 17.4)
Solicited injection site reaction	129/168	76.8	(69.7 ; 82.9)	132/165	80.0	(73.1 ; 85.8)
9vHPV	113/168	67.3	(59.6 ; 74.3)	125/165	75.8	(68.5 ; 82.1)
Tdap-IPV	118/168	70.2	(62.7 ; 77.0)	117/164	71.3	(63.8 ; 78.1)
Grade 3 injection site reaction	18/168	10.7	(6.5 ; 16.4)	17/165	10.3	(6.1 ; 16.0)
9vHPV	13/168	7.7	(4.2 ; 12.9)	16/165	9.7	(5.6 ; 15.3)
Tdap-IPV	13/168	7.7	(4.2 ; 12.9)	13/164	7.9	(4.3 ; 13.2)
Solicited systemic reaction	81/168	48.2	(40.5 ; 56.0)	84/165	50.9	(43.0 ; 58.8)
Grade 3 systemic reaction	10/168	6.0	(2.9 ; 10.7)	11/165	6.7	(3.4 ; 11.6)

Table 32: Solicited injection site reactions after vaccine injection at Visit 2, by maximum intensity during the solicited period - SafAS2

		Group 1 (N=169)			Group 2 (N=168)		
Participants experiencing at least one:	**Maximum intensity:**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
9vHPV							
Injection site Pain	Any	113/168	67.3	(59.6 ; 74.3)	125/165	75.8	(68.5 ; 82.1)
	Grade 1	62/168	36.9	(29.6 ; 44.7)	68/165	41.2	(33.6 ; 49.1)
	Grade 2	38/168	22.6	(16.5 ; 29.7)	41/165	24.8	(18.5 ; 32.2)
	Grade 3	13/168	7.7	(4.2 ; 12.9)	16/165	9.7	(5.6 ; 15.3)
Injection site Erythema	Any	7/168	4.2	(1.7 ; 8.4)	3/165	1.8	(0.4 ; 5.2)
	Grade 1	6/168	3.6	(1.3 ; 7.6)	3/165	1.8	(0.4 ; 5.2)
	Grade 2	1/168	0.6	(0 ; 3.3)	0/165	0	(0 ; 2.2)
	Grade 3	0/168	0	(0 ; 2.2)	0/165	0	(0 ; 2.2)
Injection site Swelling	Any	4/168	2.4	(0.7 ; 6.0)	3/165	1.8	(0.4 ; 5.2)
	Grade 1	3/168	1.8	(0.4 ; 5.1)	3/165	1.8	(0.4 ; 5.2)
	Grade 2	1/168	0.6	(0 ; 3.3)	0/165	0	(0 ; 2.2)
	Grade 3	0/168	0	(0 ; 2.2)	0/165	0	(0 ; 2.2)
Tdap-IPV							
Injection site Pain	Any	116/168	69.0	(61.5 ; 75.9)	117/164	71.3	(63.8 ; 78.1)
	Grade 1	60/168	35.7	(28.5 ; 43.5)	65/164	39.6	(32.1 ; 47.6)
	Grade 2	43/168	25.6	(19.2 ; 32.9)	39/164	23.8	(17.5 ; 31.0)
	Grade 3	13/168	7.7	(4.2 ; 12.9)	13/164	7.9	(4.3 ; 13.2)
Injection site Erythema	Any	9/168	5.4	(2.5 ; 9.9)	5/164	3.0	(1.0 ; 7.0)
	Grade 1	7/168	4.2	(1.7 ; 8.4)	4/164	2.4	(0.7 ; 6.1)
	Grade 2	2/168	1.2	(0.1 ; 4.2)	1/164	0.6	(0 ; 3.4)
	Grade 3	0/168	0	(0 ; 2.2)	0/164	0	(0 ; 2.2)
Injection site Swelling	Any	9/168	5.4	(2.5 ; 9.9)	3/164	1.8	(0.4 ; 5.3)
	Grade 1	9/168	5.4	(2.5 ; 9.9)	3/164	1.8	(0.4 ; 5.3)
	Grade 2	0/168	0	(0 ; 2.2)	0/164	0	(0 ; 2.2)
	Grade 3	0/168	0	(0 ; 2.2)	0/164	0	(0 ; 2.2)

Table 33: Solicited systemic reactions after vaccine injection at Visit 2, by maximum intensity during the solicited period – SafAS2

Participants experiencing at least one:	Maximum intensity:	Group 1 (N=169) n/M	%	(95% CI)	Group 2 (N=168) n/M	%	(95% CI)
Fever	Any	6/168	3.6	(1.3 ; 7.6)	7/165	4.2	(1.7 ; 8.5)
	Grade 1	6/168	3.6	(1.3 ; 7.6)	5/165	3.0	(1.0 ; 6.9)
	Grade 2	0/168	0	(0 ; 2.2)	1/165	0.6	(0 ; 3.3)
	Grade 3	0/168	0	(0 ; 2.2)	1/165	0.6	(0 ; 3.3)
Headache	Any	37/168	22.0	(16.0 ; 29.1)	40/165	24.2	(17.9 ; 31.5)
	Grade 1	23/168	13.7	(8.9 ; 19.8)	23/165	13.9	(9.0 ; 20.2)
	Grade 2	12/168	7.1	(3.7 ; 12.1)	13/165	7.9	(4.3 ; 13.1)
	Grade 3	2/168	1.2	(0.1 ; 4.2)	4/165	2.4	(0.7 ; 6.1)
Malaise	Any	40/168	23.8	(17.6 ; 31.0)	26/165	15.8	(10.6 ; 22.2)
	Grade 1	25/168	14.9	(9.9 ; 21.2)	15/165	9.1	(5.2 ; 14.6)
	Grade 2	13/168	7.7	(4.2 ; 12.9)	6/165	3.6	(1.3 ; 7.7)
	Grade 3	2/168	1.2	(0.1 ; 4.2)	5/165	3.0	(1.0 ; 6.9)
Myalgia	Any	67/168	39.9	(32.4 ; 47.7)	61/165	37.0	(29.6 ; 44.8)
	Grade 1	36/168	21.4	(15.5 ; 28.4)	30/165	18.2	(12.6 ; 24.9)
	Grade 2	23/168	13.7	(8.9 ; 19.8)	21/165	12.7	(8.1 ; 18.8)
	Grade 3	8/168	4.8	(2.1 ; 9.2)	10/165	6.1	(2.9 ; 10.9)

Unsolicited AEs in the SafAS2

Table 34: Summary of unsolicited AEs within 30 days (from D1 to D31) after any vaccine injections at Visit 2 - Safety Analysis Set for vaccination at Visit 2

Participants experiencing at least one:	Group 1 (N=169) n	%	(95% CI)	n AEs	Group 2 (N=168) n	%	(95% CI)	n AEs
Immediate unsolicited AE	0	0	(0 ; 2.2)	0	0	0	(0 ; 2.2)	0
Grade 3 immediate unsolicited AE	0	0	(0 ; 2.2)	0	0	0	(0 ; 2.2)	0
Immediate unsolicited AR	0	0	(0 ; 2.2)	0	0	0	(0 ; 2.2)	0
Grade 3 immediate unsolicited AR	0	0	(0 ; 2.2)	0	0	0	(0 ; 2.2)	0
Unsolicited AE	34	20.1	(14.4 ; 27.0)	42	27	16.1	(10.9 ; 22.5)	37
Grade 3 unsolicited AE	1	0.6	(0 ; 3.3)	2	0	0	(0 ; 2.2)	0
Unsolicited AR	7	4.1	(1.7 ; 8.3)	8	8	4.8	(2.1 ; 9.2)	10
Grade 3 unsolicited AR	0	0	(0 ; 2.2)	0	0	0	(0 ; 2.2)	0
Unsolicited injection site AR	4	2.4	(0.6 ; 5.9)	4	8	4.8	(2.1 ; 9.2)	9
After injection of 9vHPV	3	1.8	(0.4 ; 5.1)	3	3	1.8	(0.4 ; 5.1)	3
After injection of Tdap-IPV	1	0.6	(0 ; 3.3)	1	6	3.6	(1.3 ; 7.6)	6
Grade 3 unsolicited injection site AR	0	0	(0 ; 2.2)	0	0	0	(0 ; 2.2)	0
After injection of 9vHPV	0	0	(0 ; 2.2)	0	0	0	(0 ; 2.2)	0
After injection of Tdap-IPV	0	0	(0 ; 2.2)	0	0	0	(0 ; 2.2)	0
Unsolicited systemic AE	31	18.3	(12.8 ; 25.0)	38	23	13.7	(8.9 ; 19.8)	28
Grade 3 unsolicited systemic AE	1	0.6	(0 ; 3.3)	2	0	0	(0 ; 2.2)	0
Unsolicited systemic AR	3	1.8	(0.4 ; 5.1)	4	1	0.6	(0 ; 3.3)	1
Grade 3 unsolicited systemic AR	0	0	(0 ; 2.2)	0	0	0	(0 ; 2.2)	0
SAE	0	0	(0 ; 2.2)	0	0	0	(0 ; 2.2)	0
Grade 3 SAE	0	0	(0 ; 2.2)	0	0	0	(0 ; 2.2)	0

Group 1: MenACYW conjugate vaccine on D01 and 9vHPV + Tdap-IPV vaccines on D31. Group 2: Nimenrix on D01 and 9vHPV + Tdap-IPV vaccines on D31.
n: number of participants experiencing the endpoint listed in the first column
n AEs: number of AEs
AR: Reactions related to the study vaccine
Immediate unsolicited AE' is collected only for immediate unsolicited systemic AE.
Unsolicited AE' also includes immediate and serious unsolicited AEs.

Unsolicited AEs within 30 days of vaccination were mainly reported in the following SOCs: “Infections and infestations” (12.4% [21/169]) in Group 1 and “Infections and infestations” (5.4% [9/168]) in Group 2. Most unsolicited AEs started during the time period ≥ D16 and resolved after 8-14 days in Group 1. Most unsolicited AEs started during the time period D1-D4, and resolved after 1-3 days and 8-14 days in Group 2. At least 1 Grade 3 unsolicited AE was reported in 0.6% (1/169) of participants in Group 1.

2.3.3. Discussion on clinical aspects

The main purpose of study MEQ00071, a Phase IIIb study conducted in Spain, Italy, Hungary, and Singapore, was to compare MenACYW conjugate vaccine, a quadrivalent meningococcal conjugate vaccine, with a licensed quadrivalent meningococcal polysaccharide (Groups A, C, W- 135, Y) conjugate vaccine (Nimenrix) in the adolescent population. Nimenrix is widely used in several countries, but no data on MenACYW conjugate vaccine versus Nimenrix has been generated in the adolescent population to date. The MEQ00071 study included both MenC naive adolescents and adolescents who have received at least one dose of a MenC vaccine before 2 years of age, in order to explore the impact of MenC priming in infancy on MenC immune responses induced by the MenACYW conjugate vaccination in adolescents. Additionally, this study has also generated co-administration data on MenACYW conjugate vaccine with 2 adolescent vaccines: 9-valent human papilloma virus (9vHPV) vaccine and tetanus, diphtheria, acellular pertussis, and inactivated poliomyelitis (Tdap-IPV) vaccine. MEQ00071 was conducted between 16 March 2021 (first participant first visit) and 11 May 2022 (last participant last visit).

The MAH intends to submit a Type II variation with Product Information update in Q1 2024 with the MEQ00071 study data. Of note, study MEQ00071 is not included in the MenQuadfi Paediatric Investigational Plan (EMA procedure number: EMEA-001930-PIP01-16-M04). MenQuadfi is currently indicated in the European Union from the age of 12 months and older against invasive meningococcal disease caused by Neisseria meningitidis serogroups A, C, W and Y.

Population: Overall, there were more male (67.4%) than female (32.6%) subjects. The male/female ratios were 2.53 in Group 1, 2.04 in Group 2, and 1.60 in Group 3. Especially the imbalance across groups is critically noted. Furthermore, there were slightly more MenC primed participants in Group 3 (74.4%) than in Group 1 (69.4%) and Group 2 (68.8%). This imbalance across groups had an impact on study results with respect to antibody titers for serogroup C. Therefore, separate analyses were provided for MenC-primed and MenC-naive subjects which is appreciated (see discussion below).

Tdap-IPV vaccines are licensed in several member states and participants were excluded when having been vaccinated with Tdap-IPV vaccines within the previous 3 years before enrolment. However, it is not clear if locally recommended vaccination schedules / basic immunisation schedules have been completed. Nevertheless, nearly all participants had a vaccination history against Tetanus (96.0, 98.8, and 97.4% in Groups 1, 2, and 3, respectively), Diphtheria (96.0, 98.8, 97.4%), Pertussis (96.0, 98.8, 97.4), and Polio (96.0, 98.8, 97.4%). Gardasil9 (9vHPV) is approved centrally in the EU and recommended for subjects from the age of 9 years. Participants previously having received a human papilloma virus (HPV) vaccination were excluded from enrolment, which can be followed.

Protocol deviations: During internal data review, it was discovered that 144 participants were wrongly enrolled with unblinding group data at the Sponsor level. The Applicant states that after investigation, it was determined that this major deviation had no impact on the study conduct regarding the safety assessment and data collection, and the immunology data analysis. Apparently, no unblinding occurred at the site level (i.e., no unblinding data were accessible for investigators and no sample for immunogenicity analysis has been sent to the laboratory) at that time. In order to clarify any possible impact on safety data analysis, a sensitivity analysis was provided with only subjects included in the Overall Safety Analysis Set that were not impacted by the unblinding issue. Although the sample size decreased from 171 to 99 subjects in non-impacted Group 1 and from 171 to 100 in the non-impacted Group 2, the rates of participants experiencing at least 1 safety event were similar to the “compromised” Overall Safety Set. In fact, the rate of only a few parameters increased ≥5% between the non-impacted to the “compromised” Overall Safety Analysis Set in Group 1 (solicited injection site reactions after injection of MenACWY (50.5% to 57.4%), unsolicited AE (35.4% to 40.4%), unsolicited AR (4.0% to 11.1%), unsolicited injection site AR (2.0% to 7.6%)) and Group 2

(unsolicited AE (35.4% to 28.7%)). It is critically noted that especially in Group 1 an increase was observed, however, no specific impact on safety data based on the unblinding issue on Sponsor level could be identified.

The most frequently reported major protocol deviation was “IMP administered but not as per protocol” in 48 participants (10.4%). Indeed, 48 participants were wrongly administered with Tdap-IPV and/or 9vHPV vaccines in the same arm as MenACYW conjugate vaccine. This deviation would especially compromise the evaluation of local reactions in patients of Group 3, but only 1 subject in Group 3 (and 23 and 24 subjects in Groups 1 and 2, respectively) were reported with “IMP administered but not as per protocol”. The deviation is not seen overly critical for Groups 1 and 2 with respect to the time between vaccinations (i.e., 30 days), which allows for a distinct assessment of the local safety profile. A safety overview has been provided with these subjects that were affected by erroneous administration excluded. No critical deviation to the full set of safety data was evident.

Primary immunogenicity objective:

In the PPASM, non-inferiority of the seroprotection rate (serum bactericidal assay using human complement [hSBA] titer ≥ 1:8) to meningococcal serogroups A, C, W, and Y following the administration of a single dose of MenACYW conjugate vaccine (Group 1) compared to a single dose of Nimenrix (Group 2) was demonstrated for MenACYW conjugate vaccine versus Nimenrix. Of note, for the primary analysis the immunogenicity of both vaccines thirty days after vaccination when given alone in Groups 1 and 2 were compared. Results for Group 3 (with concomitant 9vHPV and Tdap-IPV vaccination) are provided below for completeness, although formally not being part of the planned primary endpoint analysis. After vaccination, the proportion of participants who achieved hSBA titers ≥ 1:8 was comparable and high across all groups and serogroups: 97.5%, 92.5%, and 91.2% (Groups 1, 2, and 3, respectively) in serogroup A, 100%, 95.0%, and 99.1% in serogroup C, 100%, 98.8%, and 99.1% in serogroup W, and 99.4%, 98.1%, and 100% in serogroup Y. This indicates a sufficient protection against infection for all vaccination schemes and both meningococcal vaccines applied in the study. Still, the difference between Groups 1 and 2 in seroprotection of serogroups A and B was slightly higher (~5.0%) than for serogroups W and Y (~1.2). The primary objective was also demonstrated in the hSBA FAS. However, it should be noted that the proportion of participants who had hSBA titers ≥ 1:8 at baseline was already high across all Groups, especially in serogroups A and C: 56.3%, 50.6%, and 58.9% in serogroup A, 41.1%, 35.6%, and 41.6% in serogroup C, 22.6%, 28.6%, and 26.8% in serogroup W, and 9.4%, 15.5%, and 6.2% in serogroup Y for study Groups 1, 2 and 3, respectively.

Secondary immunogenicity objectives:

In addition to seroprotection rates, the immune responses against meningococcal serogroups A, C, W, and Y 30 days after vaccination with meningococcal vaccines administered alone (Group 1, hSBA PPASM) were higher to that elicited by Nimenrix (Group 2) and MenQuadfi+TdapIPV+9vHPV (Group 3) in terms of geometric mean titers (GMTs) and vaccine seroresponse rates for all 4 serogroups, except for GMTs against serogroup Y which were comparable in Groups 1 and 3.

GMTs were 78.2, 56.0, and 42.2 measured 30 days after vaccination with MenACWY vaccines administered alone for serogroup A (in Groups 1, 2, and 3, respectively), 2294, 619, and 1938 for serogroup C, 134, 64.6, and 74.6 for serogroup W, and 169, 84.8, and 171 for serogroup Y (PPASM). High titer levels are noted for serogroup C, most likely based on the high rate of MenC-primed subjects in the study, and especially for Groups 1 and 3, which also had the highest rate in MenC-primed subjects. Seroresponse (defined as post-vaccination titer ≥1:16 for participants with pre-vaccination hSBA titer < 1:8, or a postvaccination titer ≥4-fold increase from baseline for participants with pre-vaccination hSBA titer ≥1:8) was observed in 88.0%, 75.5%, and 63.4% of subjects after vaccination

for serogroup A, 99.4%, 88.8%, and 97.3% for serogroup C, 93.1%, 81.4%, and 85.7% for serogroup W, and 98.7%, 88.1%, and 99.1% for serogroup Y in study Groups 1-3, respectively.

Reason for the slightly higher response in antibody titers for group 1 and 3 compared to group 2 could be related to the higher meningococcal capsular polysaccharide concentrations in MenQuadfi compared to Nimenrix (i.e., 10 µg vs. 5 µg per serogroup) as well as the higher concentration of the tetanus toxoid protein carrier in MenQuadfi (55 µg vs. 44 µg).

In MenC-naïve participants, baseline GMTs of serogroup C were 4.59 and 3.15 (in Groups 1 and 2, respectively) measured at D01, and increased to 489 and 29.0 at D31. This converts to GMT ratios (GMTRs) of 106 and 9.22 for Groups 1 and 2, indicating a higher response to MenQuadfi compared to Nimenrix. As can be expected, MenC-primed participants had higher serogroup C baseline GMTs of 7.30 and 7.06 measured at D01 which increased to 4222 and 2361 at D31 and which converts to much higher GMTRs of 597 and 337, respectively. Therefore, the proportion of MenC-primed participants, who had MenC hSBA titers ≥1:8 at baseline (i.e., seroprotection), was comparable and already high between Groups 1 and 2 (46.9% vs. 45.9). After vaccination (D31), seroprotection for serogroup C in MenC-primed participants was 100% in both groups. Contrarily, the proportion of MenC-naive participants, who had MenC seroprotection at baseline, was considerably lower in Groups 1 and 2 (26.7% vs. 12.2%). Nevertheless, seroprotection increased to 100% in Group 1 (MenQuadfi), while it increased only to 85.7% in Group 2 (Nimenrix) after vaccination (D31) in MenC-naïve participants. In general, the MenC immune response 30 days after vaccination was highest with MenQuadfi (Group 1) in MenC-primed participants. Similar results were observed in the hSBA FAS and rSBA PPASM.

The immune responses for meningococcal serogroups A, C, W, and Y with MenACYW conjugate vaccine administered alone (Groups 1 and 2) or concomitantly with 9vHPV + Tdap-IPV vaccines (Group 3) was measured on D31 (i.e., before 9vHPV and Tdap-IPV vaccinations in Groups 1 and 2, but 30 days after concomitant vaccination in Group 3). GMTs of MenQuadfi alone (Group 1) are considerably higher than MenQuadfi administered concomitantly with childhood vaccinations (Group 3) for serogroups A, C and W: GMTs are 78.2, 56.0, and 42.2 (serogroup A in Groups 1, 2, and 3, respectively), 2294, 619, and 1938 (serogroup C), 134, 64.6, and 74.6 (serogroup W), and 169, 84.8, and 171 (serogroup Y). The calculated 95%CIs are not overlapping for serogroups A and W. Similarly, seroresponses were considerably higher in Group 1 vs. Group 3 for serogroups A, C and W: Seroresponse rates are 88.0%, 75.5% and 63.4% (serogroup A), 99.4%, 88.8%, and 97.3% (serogroup C), 93.1%, 81.4%, and 85.7% (serogroup W), and 98.7%, 88.1%, and 99.1% (serogroup Y). The calculated 95%CIs are not overlapping for serogroup A. It is concluded that the immune response induced by MenQuadfi was higher or comparable when MenACYW conjugate vaccine was administered alone versus concomitantly with 9vHPV+Tdap-IPV vaccines. Based on these data, the concomitant vaccination during adolescence (administered together with the tested vaccines) appears principally acceptable, since seroprotection rates 30 days after vaccination were high also for Group 3 (91.2%, 99.1%, 99.1% and 100% of subjects in Group 3 compared to 97.5%, 100%, 100% and 99.4% in Group 1 for serogroups A, C, W and Y, respectively), but not favourable compared to the sequential administration, with respect to the expected antibody response for serogroups A, C and W. Thus, the information on lower titer response after coadministration should be reported in the PI once a coadministration of MenQuadfi and 9vHPV+Tdap-IPV is intended to be included.

The post-dose 9vHPV antibody responses based on pre-dose are roughly comparable between groups, although there is a clear trend for a lower response to presented HPV antigens when MenQuadfi is concomitantly administered with Tdap-IPV (i.e., response with MenQuadfi+9vHPV sequential (Group 1) > Nimenrix+9vHPV sequential (Group 2) > MenQuadfi+9vHPV concomitantly (Group 3)). As mentioned by the Applicant, no conclusions about clinical relevance of absolute post-dose GMs can be drawn since the participants were given only the first dose of what is ultimately a 2 or 3-dose vaccination regimen. Of note, also the detection method used for HPV testing has changed

from the one described in the protocol (Fluorescent Luminex multiplex instead of Sulfotag multiplex MSD) due to unavailability of the technique at the CRO. According to the Applicant, this change does not modify the assay principle (HPV IgG LIA assay) and the measurement technique for HPV Ab titer. Cut-off values used for serostatus definition were adapted to the technique used. However, no definite conclusions on HPV immunity can be derived due to the incomplete vaccination scheme and uncertainty regarding the switch of the utilized assay.

All geometric means of Tdap-IPV antibody titers or antibody concentrations were higher post-dose, except for the Anti-Tetanus component in the Tdap-IPV vaccine when sequentially administering a MenACWY vaccine with the Tdap-IPV vaccine (Groups 1 and 2). Indeed, the GMT concentration of Anti-Tetanus antibodies decreased (rather than increased) from 25.5 and 18.4 IU/mL at baseline to 17.3 and 16.1 IU/mL in groups 1 and 2 after vaccination, respectively. Contrarily, antibody concentrations increased in Groups 3 from 0.7 to 48.7 IU/mL (as intended). Of note, the GMT was substantially lower in Group 3 before Tdap-IPV vaccination than in Groups 1 and 2 (pre-dose GMTs of 25.5, 18.4 and 0.708 were reported for Groups 1, 2 and 3, respectively). According to the Applicant, this was expected as 30 days before Tdap-IPV vaccination participants in Group 1 and Group 2 received MenQuadfi or Nimenrix, which are both tetanus toxoid-conjugated-vaccines. It can be followed that a prior vaccination with a tetanus toxoid-conjugated vaccine (e.g., MenQuadfi or Nimenrix) can increase antibody titer levels in subjects. However, it is not clear why titer levels decrease after vaccination with Tdap-IPV, as evident from Groups 1 and 2. This effect should be thoroughly discussed once a coadministration of MenQuadfi and Tdap-IPV is intended to be included in the PI. Importantly, almost all patients across all groups had titer levels ≥1 IU/mL after vaccination with Tdap-IPV (only 1/149 subjects in group 1 had levels below 1, but still ≥0.1 IU/mL), which underlines the existing protection against tetanus infection. The post-dose responses of Tdap-IPV (other than Anti-Tetanus antibodies) based on pre-dose levels are principally comparable between groups, although there is a trend for lower Tdap-IPV responses when MenQuadfi is concomitantly administered with Tdap-IPV (MenQuadfi+TdapIPV sequential (Group 1) > Nimenrix+TdapIPV sequential (Group 2) > MenQuadfi+TdapIPV concomitantly (Group 3)). Especially Anti-Polio type 1 and type 3 GMT ratios (post-dose based on pre-dose) in group 3 were 2-3-fold lower compared to Groups 1 and 2, which have followed the sequential administration of vaccines. A similar, but less pronounced, trend was also observed for Anti-Diphteria titer level ratios (with lower levels in group 3 and non-overlapping 95%CIs in GMT ratios with Groups 1 and 2). Importantly, all subjects had protective Anti-Polio-titer levels (i.e., ≥1:8) for all three types and the majority of subjects (>90%) also had protective anti-Diphteria titer levels (i.e., ≥1 IU/mL). Seroresponse of Anti-PT, Anti-FHA and Anti-PRN titers appear mildly lower in group 3 compared to groups 1 and 2, but 95%CIs are overlapping.

Thus, post-dose response of GMs of antibody concentration/titers against antigens contained in the Tdap-IPV vaccine are still considered clinically relevant if administered concomitantly with MenQuadfi (Group 3). Still, a lower response in antibody titers should be anticipated for Anti-Polio-type 1 and type 3, as well as anti-Diphtheria when 9vHPV and Tdap-IPV are administered concomitantly with MenQuadfi (compared to a sequential administration). Furthermore, the decrease in anti-tetanus antibodies upon vaccination with Tdap-IPV should be discussed by the Applicant when submitting the planned Type II Variation in Q1 2024.

Long-term antibody persistence data were not generated in the study.

Safety

Throughout the study >97% of subjects were exposed to the intended vaccines at planned visits. The Overall SafAS is considered the most informative analysis set for the comparison of local reactions, as events can be related to the exact vaccine that was received. However, systemic events are more

suitable to be assessed in the SafAS1 and SafAS2 as events can be related at least to the visit with distinct vaccination schedule.

There were no AEs that caused participants to discontinue from the study and no SAEs within 30 days of vaccination in any group. There was 1 SAE reported throughout the study for 1 participant (0.6%) in Group 2. The participant experienced type 1 diabetes mellitus, which was classified as not vaccine-related, which can be followed. There were no AESIs and no deaths throughout the study.

Solicited reactions

No immediate unsolicited AEs were reported within 30 minutes of vaccination in any group. The solicited reactions within the solicited period after any vaccine injections (Overall SafAS) were frequent (90.5, 88.8, and 95.7% for Groups 1, 2, and 3, respectively) and tended to be more frequent in Group 3 (concomitant administration of MenQuadfi + 9vHPV + Tdap-IPV). The general trend of a higher rate in subjects with events in group 3 is also reflected in reported frequencies for Grade 3 solicited reactions (18.9, 15.3, and 25.9%). Similarly, solicited reactions within 7 days after vaccine injection at Visit 1 (SafSA1) are comparable between Groups 1 and 2, while nearly every participant in Group 3 had a solicited reaction (68.6, 65.3, and 95.7% in Groups 1, 2, and 3, respectively) and a high proportion of subjects had grade 3 solicited reactions in that group (8.3, 8.2, and 25.9% in Groups 1, 2, and 3, respectively). The rate of subjects with solicited reactions after vaccine injection at Visit 2 (SafSA2) was comparable between groups (79.2 and 82.4% with event as well as 11.9 and 11.5% with grade 3 event in groups 1 and 2, respectively).

Especially solicited injection site reactions were frequent after any vaccination (Overall SafAS; 88.2, 82.9, and 93.1%) and events were mostly related to the 9vHPV and/or Tdap-IPV vaccines (with around 10-20% more subjects reporting specific injection site after the routine paediatric vaccines compared to MenQuadfi and Nimenrix, see following). The most frequently reported solicited injection site reaction within 7 days following any vaccination was pain in all 3 groups, again, more frequently related to the 9vHPV (67.3, 75.8, and 83.6%) and Tdap-IPV (69.0, 71.3, and 81.9) vaccines than MenQuadfi (53.8% in Group 1 and 59.5% in Group 3) or Nimenrix (51.2% in Group 2). Similarly, grade 3 injection site pain was higher with 9vHPV (7.7, 9.7, and 12.9%) and Tdap-IPV (7.7, 7.9, and 12.1%) than with MenQuadfi (2.4% in Group 1 and 1.7% in Group 3) or Nimenrix (2.4% in Group 2), and was especially frequent in participants of Group 3 who had received 9vHPV and Tdap-IPV concomitantly with MenQuadfi. In general, a total of 62 participants reported at least 1 Grade 3 solicited injection site reaction within 7 days of vaccination (14.2, 11.2, and 16.4%). Notably, the rates of subjects that reported injection site erythema (11.2, 1.8, and 9.5%) and swelling (10.1, 4.1, and 10.3%) were considerably lower in Group 2 with Nimenrix. Similarly, solicited injection site reactions reported for the SafAS1 are comparable between Groups 1 and 2, while most participants in Group 3 had a solicited injection site reaction (57.4, 52.9, and 93.1% in Groups 1, 2, and 3, respectively). The higher rate of solicited injection site reaction in subjects of Groups 1 and 2 (who received 9vHPV+Tdap-IPV 30 days after the MenACWY vaccines) is also reflected in SafAS2 (76.8% and 80% in Groups 1 and 2, respectively).

The most frequently reported solicited systemic reactions within 7 days of any vaccination (Overall SafAS) were myalgia (49.7, 47.6, and 57.8%), headache (44.4, 37.6, and 44.8%), and malaise (38.5, 28.2, and 36.2%). No distinction between vaccines, that were provided at the same visit, is possible for systemic reactions, but considering also the SafAS1 (50.9, 45.9 and 71.6% of subjects with systemic reactions in Groups 1, 2, and 3, respectively) and the SafAS2 (48.2 and 50.9% in Groups 1 and 2, respectively) it can be concluded that around 20% more subjects experienced a solicited systemic event after coadministration of MenQuadfi with 9vHPV+Tdap-IPV compared to MenQuadfi, Nimenrix or 9vHPV+Tdap-IPV alone. Solicited systemic reactions after vaccine injection at Visit 1 (SafSA1) were mostly headache (35.1, 25.9 and 44.8% of subjects with event in groups 1-3,

respectively), malaise (27.2, 18.8 and 36.2% of subjects with event in groups 1-3, respectively) and myalgia (30.2, 31.2 and 57.8% of subjects with event in groups 1-3, respectively) with substantial differences across groups and highest rates in Group 3. The difference between Group 1 and 2 is mostly related to grade 1 and 2 events, but not evident for grade 3 events. However, Group 3 also had a higher rate of grade 3 events compared to both other groups.

In general, the trend of more subjects with local and systemic reactions in Group 3 is somewhat expected, as reactions of either vaccine have to be anticipated at the same visit. Tdap-IPV and 9vHPV appear more reactogenic compared to both meningococcal vaccines. Furthermore, it is concluded that MenQuadfi appears more reactogenic compared to Nimenrix, with a higher rate of subjects reporting solicited events, especially injection site erythema and swelling as well as headache and malaise.

Unsolicited AEs

Unsolicited AE within 30 days after any vaccine injections (overall SafAS) were comparable between groups, albeit slightly higher in Group 1 (40.4, 28.7, and 31.9% for Groups 1, 2, and 3). However, the SafAS1 and SafAS2 allow for a better relation of events to the vaccinations of a specific visit.

Unsolicited AEs in the SafAS1 and SafAS2 indicate a mildly higher rate of events that were related to Menquadfi (28.7% of subjects reported an event in Group1 after visit 1) compared to Nimernrix (18.1% of subjects reported an event in Group 2 after visit 1) or 9vHPV+Tdap-IPV (20.1% and 16.1% of subjects reported an event in Group 1 and 2 after visit 2, respectively). However, the highest rate was observed after visit 1 in subjects that have received the coadministration of Menquadfi with 9vHPV+Tdap-IPV (31.9%), which appears expectable as reactions of either vaccine have to be anticipated at the same visit and in line with systemic solicited reactions reported above. Furthermore, more subjects appear to be affected by unsolicited events after vaccination with Menquadfi compared to Nimenrix (refer to Groups 1 and 2 after visit 1). Unsolicited AEs within 30 days of vaccination after visit 1 (SafAS1) were mainly reported (i.e. in ≥5% of subjects) in the following SOCs: “Infections and infestations” (11.7%) and “General disorders and administration site conditions” (9.4%) in Group 1; “Infections and infestations” (7%) in Group 2; and “Infections and infestations” (12.1%), “General disorders and administration site conditions” (9.5%), and “Gastrointestinal disorders” (7.8%) in Group 3. After visit 2 (SafAS2) only the SOC “Infections and infestations” was reported by ≥5% of subjects (12.4% and 5.4% in groups 1 and 2, respectively). Most unsolicited AEs started during the time period D1-D4 and resolved within 7 days in all Groups . At least 1 Grade 3 unsolicited AE was reported in 1.6% of participants in Group 1, 0.6% of participants in Group 2, and 2.6% of participants in Group 3 after visit 1 (SafAS1).

Unsolicited AR were concluded in 8.8% of participants in Group 1, 3.5% of participants in Group 2, and 10.3% of participants in Group 3 after the first visit (SafAS1). Unsolicited ARs after the second visit were reported by 4.1% and 4.8% in groups 1 and 2, respectively. Thus, it appears that the highest rate of AR has to be anticipated for MenQuadfi. However, systemic ARs were not very frequent after visit 1 (2.3, 1.2 and 1.7% in Groups 1-3, respectively) or visit 2 (1.8 and 0.6% in Groups 1 and 2, respectively). The main unsolicited injection site ARs reported after vaccination at visit 1 and 2 were in the SOC “General disorders and administration site conditions” with a comparable pattern of PTs for all groups, but with the highest rate in Group 3 and lowest rate in Group 2 after the first visit (6.4, 2.3 and 9.5% in Groups 1-3 after visit 1 as well as 4.1% and 4.8% for Groups 1 and 2 after visit 2, respectively). All unsolicited systemic ARs within 30 days of vaccination after visit 1 or 2 were single PT events within groups. No participants reported any Grade 3 unsolicited systemic ARs within 30 days of vaccination in any group.

It is concluded that a higher rate of subjects might be affected by unsolicited AEs after vaccination with MenQuadfi compared to Nimenrix, and that the rate of subjects affected might be even increased when MenQuadfi is given at the same visit with 9vHPV+Tdap-IPV. Still, the overall reactogenicity and safety

profiles appear manageable and comparable between MenACYW conjugate vaccine administered sequentially (Group 1) or concomitantly with 9vHPV+Tdap-IPV vaccines (Group 3) and Nimenrix administered sequentially with 9vHPV + Tdap-IPV vaccines (Group 2).

3. Rapporteur's overall conclusion and recommendation

On 06 October 2023, the MAH submitted a completed paediatric study MEQ00071. The study was completed on 11 May 2022.

Antibody titers 30 days after vaccination with MenQuadfi were sufficiently high to assume protection and were slightly higher compared to the vaccination with Nimenrix. In terms of antibody response, the sequential administration of MenQuadfi before 9vHPV+Tdap-IPV appears to be favourable over the concomitant administration. However, protection rates were high for either setup. It is noted that tetanus titer levels decrease after vaccination with Tdap-IPV in subjects that were vaccinated with MenQuadfi (and Nimenrix) 30 days before. This effect should be thoroughly discussed once a coadministration of MenQuadfi and Tdap-IPV is intended to be included in the PI. Furthermore, a lower response in antibody titers should be anticipated for Anti-Polio-type 1 and type 3, as well as anti-Diphtheria when 9vHPV and Tdap-IPV are administered concomitantly with MenQuadfi (compared to a sequential administration).

Tdap-IPV and 9vHPV appear more reactogenic compared to both meningococcal vaccines, but MenQuadfi appears more reactogenic compared to Nimenrix, with a higher rate of subjects reporting solicited events, especially injection site erythema and swelling as well as headache and malaise. Unsolicited AEs should be anticipated for a higher proportion in subjects after vaccination with MenQuadfi compared to Nimenrix, and that rate might be even increased when MenQuadfi is given at the same visit with 9vHPV+Tdap-IPV. It is reassuring that no AEs leading to discontinuation from the study and no SAEs within 30 days of vaccination were observed in the study. One SAE of type 1 diabetes mellitus (that occurred >30 days after vaccination) is not considered vaccine-related. Also, no AESIs and no deaths were reported throughout the study.

No concerns derive from data reported from study MEQ00071 regarding the current B/R for MenQuadfi and therefore, the PAM is considered fulfilled.

☒ Fulfilled:

No regulatory action required.