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Committee for Medicinal Products for Human Use (CHMP)

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

Nimenrix

International non-proprietary name: meningococcal group A, C, W135 and Y conjugate vaccine

Procedure No. EMEA/H/C/002226/P46 048

Note

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

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London, 4th January 2016

Committee for Medicinal Products for Human Use (CHMP)

Final assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Nimenrix

International non-proprietary name: MENINGOCOCCAL GROUP A, C, W135 AND Y CONJUGATE VACCINE

Procedure no.: EMA/H/C/2226/P46 048

Marketing authorisation holder (MAH): GSK Biologicals

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LIST OF ABBREVIATIONS

10Pn-PD-DiT	GSK Biologicals' liquid 10-valent pneumococcal conjugate vaccine with protein D, diphtheria and tetanus toxoids as protein carriers and containing pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F, referred in the document as *Synflorix*
AE	Adverse Event
ANOVA	Analysis of Variance
ATP	According-To-Protocol
BCG	Bacille Calmette-Guérin
CDC	Centers for Disease Control and Prevention, United States
CI	Confidence Interval
CLIA	Chemiluminescent Immunoassay
CRM_{197}	A non-toxic mutant form of *Corynebacterium diphtheria* toxin
CRO	Contract Research Organization
DoB	Date of Birth
D	Diphtheria
DT	Diphtheria Toxoid
DTPa-HBV-IPV/Hib	Combined Diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated polio virus-*Haemophilus influenzae* type b vaccine, refered throughout the document as DTPa-HBV-IPV/Hib or *Infanrix* hexa
EBV	Epstein Barr Virus
eCRF	electronic Case Report Form
ELISA	Enzyme-Linked Immunosorbent Assay
ER	Emergency Room
ESFU	Extended Safety Follow-Up
EU	European Union

FDA	Food and Drug Administration, United States
FHA	Filamentous Haemagglutinin
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titre
GBS	Guillain-Barre Syndrome
GSK	GlaxoSmithKline
HBs	Hepatitis B Surface antigen
hSBA	Serum Bactericidal Assay/Activity using human complement
hSBA-MenA	Serum bactericidal activity against *N. meningitidis* serogroup A using human complement
hSBA-MenC	Serum bactericidal activity against *N. meningitidis* serogroup C using human complement
hSBA-MenW-135	Serum bactericidal activity against *N. meningitidis* serogroup W-135 using human complement
hSBA-MenY	Serum bactericidal activity against *N. meningitidis* serogroup Y using human complement
ICF	Informed Consent Form.
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IM	Intramuscular
IMD	Immune Mediated Disease
IRB	Institutional Review Board
IU	International Units
LAR	Legally Acceptable Representative.
MedDRA	Medical Dictionary for Regulatory Activities
MenA	*Neisseria meningitidis* serogroup A
MenACWY-TT	GSK Biologicals' meningococcal serogroups A, C, W-135, Y tetanus toxoid conjugate vaccine

MenC	*Neisseria meningitidis* serogroup C
MenW-135	*Neisseria meningitidis* serogroup W-135
MenY	Neisseria *meningitidis* serogroup Y
MMR	Measles, Mumps and Rubella
MMRV	Measles, Mumps, Rubella and Varicella
NOCI	New Onset of Chronic Illness(es)
OPA	Opsonophagocytotic Activity
PD	Protein D, a 42kD cell-surface lipoprotein which is highly conserved among capsulated and unencapsulated strains of *Haemophilus influenzae*.
PHE	Public Health England
PRN	Pertactin
PRP	Polyribosyl Ribitol Phosphate
PS	Polysaccharide
PT	Pertussis Toxoid
RDE	Remote Data Entry
rSBA	Serum Bactericidal Assay/Activity using rabbit complement
rSBA-MenA	Serum bactericidal activity against *N. meningitidis* serogroup A (using rabbit complement)
rSBA-MenC	Serum bactericidal activity against *N. meningitidis* serogroup C using rabbit complement
rSBA-MenW-135	Serum bactericidal activity against *N. meningitidis* serogroup W-135 using rabbit complement
rSBA-MenY	Serum bactericidal activity against *N. meningitidis* serogroup Y using rabbit complement
RSV	Respiratory Syncitial Virus
SAE	Serious Adverse Event

SAS	Statistical Analysis System
SBA	Serum Bactericidal Assay
SBIR	Central randomization call-in system on Internet
SPC	Summary of Product Characteristics
TCS	Tata Consulting Services
TT	Tetanus Toxoid
UK	United Kingdom
vs.	Versus
WHO	World Health Organization

1. Introduction

On 7th October 2015, the MAH submitted a completed paediatric study for Nimenrix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the Paediatric Investigation Plan, as agreed with the Paediatric Committee

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Nimenrix is a quadrivalent meningococcal polysaccharide conjugate vaccine composed of the capsular polysaccharides of Neisseria meningitidis serogroups A, C, W-135 and Y, each conjugated to tetanus toxoid.

Nimenrix was authorised via the centralised procedure on 20th April 2012 for active immunisation of individuals from the age of 12 months and above against invasive meningococcal disease caused by Neisseria meningitidis serogroups A, C, W-135 and Y. A single dose is used for immunisation from one year on.

Nimenrix bears the following indication (taken from the SPC):

4.1 Therapeutic indications

Nimenrix is indicated for active immunisation of individuals from the age of 12 months and above against invasive meningococcal diseases caused by *Neisseria meningitidis* group A, C, W-135 and Y.

Nimenrix bears the following posology (taken from the SPC):

4.2 Posology and method of administration

Posology

Nimenrix should be used in accordance with available official recommendations.

Primary vaccination:
A single 0.5 ml dose of the reconstituted vaccine is used for immunisation.

Booster vaccination:
Nimenrix may be given in subjects who have previously been vaccinated with a plain polysaccharide meningococcal vaccine (see sections 4.4 and 5.1).

Paediatric population

The safety and efficacy of Nimenrix in children under 12 months of age has not yet been established.
No data are available.

Method of administration

Immunisation should be carried out by intramuscular injection only, preferably into the deltoid muscle.
In children 12 to 23 months of age, the vaccine may also be administered in the anterolateral part of the thigh (see sections 4.4 and 4.5).

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

As agreed with the PDCO for the Nimenrix Paediatric Investigation Plan, the company has conducted a study to assess the use of Nimenrix in subjects below 12 months of age.

The company now submits the clinical study report for study MenACWY-TT-083 (EudraCT number: 2009-016841-24) in accordance with Article 46 of Regulation (EC) No 1901/2006.

Study MenACWY -TT -083 evaluates a 2-dose and a 3-dose MenACWY -TT primary vaccination schedule in infancy « 12 months). The study was conducted in Germany, Spain and Estonia.

The company states that:

- the submitted study is part of a clinical development program and that it intends to submit a type II variation (within 18 months) to include the MenACWY-TT-083 study results in the product information, proposing to extend the indication to infants below one year of age.
- in accordance with Article 16(2) of Regulation (EC) No 726/2004, the data submitted do not influence the benefit-risk balance for the above mentioned product and therefore do not require taking further regulatory action on the marketing authorisation for the above mentioned product.
- GSK Biologicals' pneumococcal conjugate vaccine (Synflorix) is also administered in the study. An article 46 application for this vaccine is being sent in parallel to the European Medicines Agency.

CHMP comment: no additional comment

2.2. Clinical aspects

2.2.1. Introduction

The company now submits the clinical study report for study MenACWY-TT-083 (EudraCT number: 2009-016841-24) in accordance with Article 46 of Regulation (EC) No 1901/2006.

2.2.2. Clinical study

Study title: Immunogenicity and safety of GSK Biologicals' meningococcal vaccine (GSK 134612) when co-administered with a pneumococcal conjugate vaccine and Infanrix hexa in healthy infants.

Study code: 113369 (MenACWY-TT-083)

EUDRACT Number: 2009-016841-24

A phase III, open, multi-country, randomized, controlled study with four parallel groups

Study initiation date: 01 July 2010
Study completion date: 10-September-2013
Data lock point (Date of database freeze): 21-August-2015
Date of report: Final: 11 September 2015

The duration of the study was about 16 months for each subject.

The company states:

- the study protocol, any amendments, the informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational centre IEC or IRB.
- overall this study was conducted in accordance with "good clinical practice" (GCP) and all applicable regulatory requirements, including the Declaration of Helsinki.

Methods

- **Study participants**

Inclusion criteria

- A male or female between, and including, 6 and 12 weeks (42-90 days) of age at the time of the first vaccination
- Born after a gestation period of at least 36 weeks

Exclusion criteria

- History of / inter-current diphtheria, tetanus, pertussis, polio, hepatitis B, Haemophilus influenzae type b disease, pneumococcal and/or meningococcal disease.
- Previous vaccination against diphtheria, tetanus, pertussis, polio, hepatitis B, Haemophilus influenzae type b, Streptococcus pneumoniae, Neisseria meningitides serogroups A, C, W-135 or Y with the exception of vaccines where the first dose could be given within the first two weeks of life according to the national recommendations (for example hepatitis B and BCG).
- Use of registered or non-registered products, as described, including immunosuppressants and immunoglobulins
- History of hypersensitivity that may be aggravated by vaccine
- Chronic disease / acute disease at time of administration

A total of 2095 subjects were enrolled in this study.

CHMP comment: the inclusion / exclusion criteria are acceptable

- **Treatments**

Subjects were assigned to one of four groups:

i. Group ACWY_3: subjects received three primary vaccination doses of MenACWY-TT vaccine at 2, 3 and 4 months of age and one booster dose of MenACWY-TT vaccine at 12 months of age.

ii. Group ACWY_2: subjects received two primary vaccination doses of MenACWY-TT vaccine at 2 and 4 months of age and one booster dose of MenACWY-TT vaccine at 12 months of age.

iii. Group MenCCRM: subjects received two primary vaccination doses of Menjugate vaccine at 2 and 4 months of age and one booster dose of Menjugate vaccine at 12 months of age (active control group).

iv. Group MenC-TT: subjects received two primary vaccination doses of NeisVac-C vaccine at 2 and 4 months of age and one booster dose of NeisVac-C vaccine at 12 months of age (active control group).

One dose of study vaccine MenACWY-TT or of one of the control vaccines (Menjugate or NeisVac-C) were to be administered according to the randomized assignment intramuscularly in the anterolateral muscle of the left thigh.

In addition, all subjects were vaccinated with Infanrix hexa and Synflorix at 2, 3, 4 and 12 months of age. Infanrix hexa and Synflorix were to be administered IM in the upper and lower anterolateral muscle of the right thigh, respectively.

For the current product, MenACWY-TT, the following formulation, presentation and lot numbers were used:

Vaccine	Formulation	Presentation (Volume*)	Lot Number (diluent lot number)
MenACWY-TT	MenA-TT conjugate 5µg;MenC-TT conjugate 5µg; MenW-TT conjugate 5µg; MenY-TT conjugate 5µg; Tetanus toxoid (total) ~44µg; Tris-HCL, pH 6.8+/-0.3 1.6 mM; Sucrose 28mg	Lyophilized pellet to be reconstituted with saline diluent (0.5 ml)	AMECA006C AMECA005A AMECA011B1 (AD02B328B) (AD02B262B2)

The following pages of this report describe the co-administered vaccines.

Synflorix (EU/1/09/508/006-7-8) [active subjstance: pneumococcal polysaccharide serotype 1, 4, 5, 6b, 7f, 9v, 14, 18c, 19f, 23f] was authorised on 30th March 2009.

The following formulation, presentation and lot numbers were used:

Vaccine	Formulation	Presentation (Volume*)	Lot Number
GSK Biologicals' 10-valent Pn-PD-DiT vaccine (*Synflorix*)	**Protein D carrier**: 1 µg of each PS for serotypes 1, 5, 6B, 7F, 9V, 14 and 23F and 3 µg for serotype 4 conjugated to PD. **Tetanus toxoid carrier**: 3 µg of capsular PS of serotypes 18C conjugated to TT. **Diphtheria toxoid**: 3 µg of capsular PS of serotype 19F conjugated to DT. Protein carrier content: ~12 µg PD, ~ 4.5 µg DT, ~ 7 µg TT 0.5 mg aluminium (Al3+) as aluminium phosphate adjuvant.	Whitish liquid in a syringe. (0.5 ml)	ASPNA031E ASPNA060F

Infanrix hexa (EU/1/00/152/001-8 & -21) [active substance: diphtheria toxoid / tetanus toxoid / Bordetella pertussis antigens (pertussis toxoid, filamentous haemagglutinin, pertactin) / hepatitis B surface antigen / poliovirus (inactivated) (type-1 (Mahoney strain), type-2 (MEF-1 strain), type-3 (Saukett strain)) / Haemophilus influenzae type-b polysaccharide] was authorised on 23rd Oct 2000.

The following formulation, presentation and lot numbers were used:

GSK Biologicals' DTPa-HBV-IPV/Hib vaccine (*Infanrix* hexa)	Diphtheria toxoid ≥ 30 IU. Tetanus toxoid ≥ 40 IU. *Bordetella pertussis* antigens Pertussis toxoid: 25 µg Filamentous haemagglutinin: 25 µg Pertactin: 8 µg. Hepatitis B surface antigen: 10 µg. Poliovirus (inactivated) type 1 (Mahoney strain): 40 D-antigen units, type 2 (MEF-1 strain): 8 D-antigen units, type 3 (Saukett strain): 32 D-antigen units. *Haemophilus influenzae* type b polysaccharide (polyribosylribitol phosphate): 10 µg conjugated to tetanus toxoid: 20-40 µg Lactose 12.6 mg, Aluminium 0.82 mg as salts	The DTPa-HBV-IPV component is a turbid white suspension in a syringe and the lyophilised Hib component is a white powder in a glass vial. (0.5 ml)	AC21B261A AC21B293A AC21B310A1 AHIBC300E AHIBC352B AHIBC393D1 AHIBC456D

Menjugate (Novartis), UK PL 13767/0023, licensed on 21st April 2004, is meningococcal group C conjugate vaccine. Menjugate has been the subject of an outgoing MRP (UK/H/0375/003) with UK as RMS and CMSs: AT, BE, DE, DK, GR, ES, FI, FR, IS, IE, IT, LU, NL, NO, PT & SE.

Active substance: Neisseria meningitidis group C (strain C11) oligosaccharide conjugated to Corynebacterium diphtheriae CRM197 protein and adsorbed on aluminium hydroxide. The product is marketed as Mejugate Kit.

The following formulation, presentation and lot numbers were used:

Novartis' meningococcal serogroup C conjugate vaccine (*Menjugate*)	10 µg of capsular oligosaccharide of meningococcal group C (strain C11) conjugated to 12.5-25 µg of *Corynebacterium diphtheriae* CRM_{197} protein. Adsorbed on aluminium hydroxide.	Lyophilised powder in vial, to be reconstituted with diluent containing aluminium hydroxide as the adjuvant (0.5 ml)	DEXTA362AY DEXTA408AY DEXTA396AY DEXTA439AY (DEXTA362AZ) (DEXTA408AZ) (DEXTA396AZ) (DEXTA439AZ)

Neis-Vac C (Baxter, acquired by Pfizer in 2014) UK PL 00057/1517, authorised on 18th July 2000. With UK as RMS, this product has been the subject of an MRP (UK/H/0435/001) with the following CMSs: AT, BE, DK, FI, FR, DE, GR, IE, IT, LU, NL, PT, ES, SE & NO.

Active substance: Neisseria meningitidis group C (strain C11) polysaccharide (de-O-acetylated)conjugated to tetanus toxoid and adsorbed on aluminium hydroxide, hydrated.

The following formulation, presentation and lot numbers were used:

Baxter's meningococcal serogroup C conjugate vaccine (*NeisVac-C*)	10 µg of capsular meningococcal group C conjugated to 10-20 µg of tetanus toxoid Aluminium 500 µg	Semi-opaque white to off-white suspension in pre-filled syringes (0.5 ml)	DEXTA365AZ DEXTA406AZ

CHMP comment: all vaccines appear to have been administered within their terms of licence and / or within an acceptable clinical investigation framework.

The dosage and administration of the study vaccines are presented in Table 6:

Table 6 Dosage and administration

Type of contact and time point	Dose	Treatment Group	Vaccine/Product	Route [1]	Site [2]	Side [3]
Visit 1 (Day 0)	1	ACWY_3	MenACWY-TT	IM	Ant T	L
	1	ACWY_2	MenACWY-TT	IM	Ant T	L
	1	MenCCRM	MenC-CRM	IM	Ant T	L
	1	MenC-TT	MenC-TT	IM	Ant T	L
	1	All groups	*Infanrix* hexa	IM	U Ant T	R
	1	All groups	*Synflorix*	IM	L Ant T	R
Visit 2 (Month 1)	2	ACWY_3	MenACWY-TT	IM	Ant T	L
	2	All groups	*Infanrix* hexa	IM	U Ant T	R
	2	All groups	*Synflorix*	IM	L Ant T	R
Visit 3 (Month 2)	3	ACWY_3	MenACWY-TT	IM	Ant T	L
	2	ACWY_2	MenACWY-TT	IM	Ant T	L
	2	MenCCRM	MenC-CRM	IM	Ant T	L
	2	MenC-TT	MenC-TT	IM	Ant T	L
	3	All groups	*Infanrix* hexa	IM	U Ant T	R
	3	All groups	*Synflorix*	IM	L Ant T	R
Visit 5 (Month 10)	4	ACWY_3	MenACWY-TT	IM	Ant T	L
	3	ACWY_2	MenACWY-TT	IM	Ant T	L
	3	MenCCRM	MenC-CRM	IM	Ant T	L
	3	MenC-TT	MenC-TT	IM	Ant T	L
	4	All groups	*Infanrix* hexa	IM	U Ant T	R
	4	All groups	*Synflorix*	IM	L Ant T	R

[1] Intramuscular (IM)
[2] Thigh (T): Upper (U) or Lower (L) or Anterolateral (Ant)
[3] Left (L)/ Right (R)

The vaccine recipients were observed closely for at least 30 minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccine(s)/product(s).

CHMP comment: all vaccines appear to have been administered with appropriate caution.

- **Objectives**

Overall: to demonstrate the non-inferiority of the immune response to Nimenrix when given intramuscularly at 2, 4 and 12 months of age or given at 2, 3, 4 and 12 months of age compared to licensed products Menjugate or NeisVac-C given intramuscularly at 2, 4 and 12 months of age.

Primary objectives:

The following co-primary objectives were to be assessed in a hierarchical manner according to the order presented below.

1. To demonstrate at 5 months of age (Visit 4) the non-inferiority of the 3-dose schedule of MenACWY-TT conjugate vaccine compared to the 2-dose schedule of the MenC-CRM197 conjugate vaccine in terms of percentage of subjects with post-primary vaccination serum bactericidal activity against N. meningitidis serogroup C using rabbit complement (rSBA-MenC) antibody titre greater than or equal to 1:8.
Criteria: the lower limit of the two-sided standardized asymptotic 95% Confidence Interval (CI) for the group difference (ACWY_3 minus MenCCRM) in the percentage of subjects with post-primary vaccination rSBA-MenC titre ≥ 1:8 is greater than or equal to the pre-defined clinical limit of -5%.

2. To demonstrate at 5 months of age (Visit 4) the non-inferiority of the 3-dose schedule of the MenACWY-TT conjugate vaccine compared to the 2-dose schedule of the MenC-TT conjugate vaccine in terms of percentage of subjects with post-primary vaccination rSBA-MenC antibody titre greater than or equal to 1:8.
Criteria: the lower limit of the two-sided standardized asymptotic 95% CI for the group difference (ACWY_3 minus MenC-TT) in the percentage of subjects with post-primary vaccination rSBA-MenC titre ≥ 1:8 is greater than or equal to the predefined clinical limit of -5%.

3. To demonstrate at 5 months of age (Visit 4) the immunogenicity of the 3-dose schedule for MenACWY-TT for serogroups A, W-135 and Y.
Criteria: the lower limit of the two-sided exact 95% CI for the percentage of subjects with post-primary vaccination rSBA antibody titre ≥ 1:8 in the ACWY_3 group is greater than or equal to the pre-defined clinical limit of 80%.

4. To demonstrate at 5 months of age (Visit 4) the non-inferiority of the 2-dose schedule of the MenACWY-TT conjugate vaccine compared to the 2-dose schedule of the MenC-CRM197 conjugate vaccine in terms of percentage of subjects with postprimary vaccination rSBA-MenC antibody greater than or equal to 1:8.
Criteria: the lower limit of the two-sided standardized asymptotic 95% CI for the group difference (ACWY_2 minus MenCCRM) in the percentage of subjects with post-primary vaccination rSBA-MenC titre ≥ 1:8 is greater than or equal to the predefined clinical limit of -5%.

5. To demonstrate at 5 months of age (Visit 4) the non-inferiority of the 2-dose schedule of the MenACWY-TT conjugate vaccine compared to the 2-dose schedule of the MenC-TT conjugate vaccine in terms of percentage of subjects with postprimary vaccination rSBA-MenC antibody titre greater than or equal to 1:8.
Criteria: the lower limit of the two-sided standardized asymptotic 95% CI for the group difference (ACWY_2 minus MenC-TT) in the percentage of subjects with postprimary vaccination rSBA-MenC titre ≥ 1:8 is greater than or equal to the predefined clinical limit of -5%.

6. To demonstrate at 5 months of age (Visit 4) the immunogenicity of the 2-dose schedule for MenACWY-TT for serogroups A, W-135 and Y.
Criteria: the lower limit of the two-sided exact 95% CI for the percentage of subjects with post-primary vaccination rSBA antibody titre ≥ 1:8 in the ACWY_2 group is greater than or equal to the pre-defined clinical limit of 80%.

Secondary objectives:

- To evaluate immunogenicity of serogroups A, C, W-135 and Y, Infanrix hexa and Synflorix
- To evaluate the safety and reactogenicity of the investigational vaccine.

CHMP comment: the objectives are acceptable

- **Study design**

A phase III, open, multi-country, randomized, controlled study with four parallel groups

Criteria for non-inferiority:

- the lower limit of the two-sided standardized asymptotic 95% CI for the group difference in the percentage of subjects with post-primary vaccination rSBA-MenC titre ≥ 1:8 is greater than or equal -5% (objectives 1, 2, 4 and 5).
- the lower limit of the two-sided exact 95% CI for the percentage of subjects with post-primary vaccination rSBA antibody titre ≥ 1:8 greater than or equal to 80%.

CHMP comment:
Discussion on the choice of the pre-defined clinical limits for declaring non-inferiority cannot be found.
The statistical analysis plan has not been included in the documentation.
[Issues may be pursued via the forthcoming variation procedure].

- **Outcomes/endpoints**

Laboratory assays and time-points

A volume of at least 6 ml (or 7ml, depending on the time point) of whole blood to provide a minimum of 3 ml (respectively 3.2 ml) of serum was to be drawn from all subjects at pre-vaccination (Day 0), one month after the last priming vaccination (Month 3), pre-booster (Month 10) and post-booster (Month 11). After centrifugation, serum samples were to be kept at –20°C until shipment to the Sponsor.

Table 7 provides an overview of the laboratory assays used for sample testing:

Table 7 Humoral Immunity (Antibody determination)

Component	Method	Kit/Manufacturer	Unit	Cut-off	Laboratory
Neisseria meningitidis Serogroup A L10 3125 Ab	rSBA	NA	1/dilution	4	Public Health England
Neisseria meningitidis Serogroup C L3v C11 Ab	rSBA	NA	1/dilution	4	Public Health England
Neisseria meningitidis Serogroup W L3v MP01240070 Ab	rSBA	NA	1/dilution	4	Public Health England
Neisseria meningitidis Serogroup Y L3v S1975 Ab	rSBA	NA	1/dilution	4	Public Health England
Neisseria meningitidis Serogroup A L10 3125 Ab	hSBA	NA	1/dilution	4	GSK Biologicals
Neisseria meningitidis Serogroup C L3v C11 Ab	hSBA	NA	1/dilution	4	GSK Biologicals
Neisseria meningitidis Serogroup W L3v MP01240070 Ab	hSBA	NA	1/dilution	4	GSK Biologicals
Neisseria meningitidis Serogroup Y L3v S1975 Ab	hSBA	NA	1/dilution	4	GSK Biologicals
Clostridium tetani.Tetanus Toxoid Ab.IgG	ELISA or multiplex	NA	IU/ml	0.1	GSK Biologicals
Corynebacterium diphtheriae.Diphtheria Toxoid Ab.IgG	ELISA or multiplex	NA	IU/ml	0.1	GSK Biologicals
Corynebacterium diphtheriae.Diphtheria Toxoid Ab	Seroneutralisation*	NA	IU/ml	0.016	GSK Biologicals
Hepatitis B Virus.Surface Ab	CLIA**	NA	mIU/ml	6.2	GSK Biologicals
Poliovirus Sabin Type 1 Ab	Seroneutralisation	NA	End point dilution 50%	8	GSK Biologicals
Poliovirus Sabin Type 2 Ab	Seroneutralisation	NA	End point dilution 50%	8	GSK Biologicals
Poliovirus Sabin Type 3 Ab	Seroneutralisation	NA	End point dilution 50%	8	GSK Biologicals
Bordetella pertussis.Pertussis Toxin Ab.IgG	ELISA or multiplex	NA	EL.U/ml	5	GSK Biologicals
Bordetella pertussis.Filamentous Hemaglutinin Ab.IgG	ELISA or multiplex	NA	EL.U/ml	5	GSK Biologicals
Bordetella pertussis.Pertactin Ab.IgG	ELISA or multiplex	NA	EL.U/ml	5	GSK Biologicals
Haemophilus influenzea type b.Polyribosyl Ribitol Phosphate Ab	ELISA or multiplex	NA	µg/ml	0.15	GSK Biologicals
Streptococcus pneumoniae.Polysaccharide 01 Ab.IgG	ELISA***	NA	µg/ml	0.15	Goldblatt
Streptococcus pneumoniae.Polysaccharide 04 Ab.IgG	ELISA	NA	µg/ml	0.15	Goldblatt
Streptococcus pneumoniae.Polysaccharide 05 Ab.IgG	ELISA	NA	µg/ml	0.15	Goldblatt
Streptococcus pneumoniae.Polysaccharide 06B Ab.IgG	ELISA	NA	µg/ml	0.15	Goldblatt
Streptococcus pneumoniae.Polysaccharide 07F	ELISA	NA	µg/ml	0.15	Goldblatt

Component	Method	Kit/Manufacturer	Unit	Cut-off	Laboratory
Ab.IgG					
Streptococcus pneumoniae.Polysaccharide 09V Ab.IgG	ELISA	NA	µg/ml	0.15	Goldblatt
Streptococcus pneumoniae.Polysaccharide 14 Ab.IgG	ELISA	NA	µg/ml	0.15	Goldblatt
Streptococcus pneumoniae.Polysaccharide 18C Ab.IgG	ELISA	NA	µg/ml	0.15	Goldblatt
Streptococcus pneumoniae.Polysaccharide 19F Ab.IgG	ELISA	NA	µg/ml	0.15	Goldblatt
Streptococcus pneumoniae.Polysaccharide 23F Ab.IgG	ELISA	NA	µg/ml	0.15	Goldblatt

rSBA = Serum Bactericidal Assay, using rabbit complement
hSBA = Serum Bactericidal Assay, using human complement
ELISA = Enzyme-linked immunosorbent assay
IU/ml = international unit per millilitre; mIU/ml = milli-international unit per millilitre
EL.U/ml = Enzyme-linked immunosorbent assay unit per millilitre
NA = Not applicable
*A subjects sample was to be tested by seroneuralization if the subject had anti-D concentrations <0.1 IU/mL by ELISA post-booster.
**Note: There was a change in the Hepatitis B assay at the time of testing from ELISA to Chemiluminescent Immunoassay (CLIA). This cut-off has been added to the tables in this report.
***Note: There was a change in the pneumococcal assay at the time of testing. The new cut-offs shown in the tables in this report for the pneumococcal antigens have been changed from 0.05 µg/ml to 0.15 µg/ml and from 0.2 µg/ml to 0.35 µg/ml, respectively.

The laboratories that performed testing for this study are listed in Table 8:

Table 8 Clinical laboratories

Laboratory	Address	Testing
Public Health England	Public Health Laboratory, Manchester Manchester Medical Microbiology Partnership, PO Box 209, 2nd Floor, Clinical Sciences Building II, Manchester Royal Infirmary, Oxford Road, Manchester, M13 9WZ -UK	rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY
GSK Biologicals Global Vaccine Clinical Laboratory, Rixensart	Biospecimen Reception - B7/44 Rue de l'Institut, 89 - B-1330 Rixensart - Belgium	hSBA-MenC, hSBA-MenY, anti-TT, anti-D, anti-D Vero-cell neutralisation, anti-PT, anti-FHA, anti-PRN and anti-PRP
GSK Biologicals Global Vaccine Clinical Laboratory, Laval Canada	Biospecimen Reception - Clinical Serology 525 Cartier blvd West - Laval - Quebec - Canada - H7V 3S8	hSBA-MenA and hSBA-MenW-135
GSK Biologicals Global Vaccine Clinical Laboratory, Wavre-Nord Noir Epine	Avenue Fleming, 20 - B-1300 Wavre - Belgium	Anti-HBs, anti-polio 1, 2, and 3*.
GOLDBLATT	University College of London Institute of Child Health 30 Guilford Street London, WC1N 1EH - UK	ELISA for pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F

*Details regarding clinical laboratories used for testing of anti-poliovirus responses will be provided in an annex report.

Statistical Methods

- **Study population / Sample size**

The target sample size was 1650 subjects evaluable for immunogenicity (412 subjects per vaccine group). Considering that approximately 20% of the enrolled subjects might have withdrawn or not been evaluable for immunogenicity, the target sample size to be enrolled was 2060 subjects (515 subjects per vaccine group).

The global power to meet all primary objectives considering a sample size of 412 evaluable subjects per group was at least 82.3%.

A total of 2095 subjects were enrolled in this study.

Six cohorts were defined for analysis:

1) Primary Total Vaccinated cohort

The Primary Total Vaccinated cohort included all vaccinated subjects during the primary phase. Thus, the Primary Total Vaccinated cohort for safety included all subjects with at least one dose of primary vaccine administration documented and the Primary Total Vaccinated cohort for immunogenicity included vaccinated subjects from primary phase for whom data concerning post-primary immunogenicity endpoint measures were available. The Total Vaccinated cohort analysis was performed per treatment actually administered.

2) Primary ATP (according to protocol) cohort for safety

The Primary ATP cohort for safety included all eligible subjects during the primary vaccination phase:

• who met all inclusion criteria and no exclusion criteria for the study,

• who had received at least one dose of study vaccine/control according to their random assignment during the primary vaccination course,

• for whom administration site of study vaccine/control was known,

• who had not received a vaccine not specified or forbidden in the protocol during the primary vaccination phase.

3) Primary ATP cohort for immunogenicity

The Primary ATP cohort for immunogenicity included all evaluable subjects from the Primary ATP cohort for safety:

• who did not receive forbidden medications as defined in the protocol;

• who had no intercurrent medical condition which might have influenced the immune response;

• who complied with the vaccination schedule for Visits 1, 2 and 3 defined in the protocol;

• who complied with the blood sample schedule for Visit 4. The interval between vaccination at Visit 3 and blood sample at Visit 4 for inclusion in the ATP cohort for immunogenicity was defined as 21 to 48 days.

4) Booster Total Vaccinated cohort

The Booster Total Vaccinated cohort included all subjects who received a booster dose at Visit 5. Thus, the Booster Total Vaccinated cohort for safety included all subjects from the primary phase with a booster dose administration documented and the Booster Total Vaccinated cohort for immunogenicity included all subjects who received a booster dose and for whom data concerning post-booster immunogenicity endpoint measures were available. The Booster Total Vaccinated cohort analysis was performed per treatment actually administered in the primary epoch.

5) Booster ATP cohort for safety

The Booster ATP cohort for safety included all eligible subjects during the booster phase of the study:

• who met all inclusion criteria and no exclusion criteria for the study;

• who had received three (for the ACWY_3 group) or two (for the ACWY_2, MenCCRM and MenC-TT groups) vaccine doses in the primary vaccination phase;

• who had received the booster vaccine dose;

• who had not received a vaccine not specified or forbidden in the protocol (subjects who received a vaccine not foreseen by the study protocol from 30 days before until 30 days after the study vaccine dose were eliminated from the Primary ATP cohort for safety if the vaccine not foreseen by the protocol was administered before the post-booster vaccination blood sample).

6) Booster ATP cohort for immunogenicity

The Booster ATP cohort for immunogenicity included all evaluable subjects from the booster ATP cohort for safety:

• who did not receive forbidden medications as defined in the protocol;

• who had no intercurrent medical condition which might have influenced the immune response;

• who complied with the vaccination schedule for Visit 5;

• who complied with the blood sample schedule for Visit 6. The interval between vaccination at Visit 5 and blood sample at Visit 6 for inclusion in the booster ATP cohort for immunogenicity was defined as 21 to 48 days.

- **Randomisation**

Randomisation was performed at GSK Biologicals, Rixensart, using MATEX, a program developed for use in SAS® (Cary, NC, USA) by GSK Biologicals.
A treatment number uniquely identified the vaccine doses to be administered to the same subject. A randomization block scheme was used for creating the randomization list to ensure that correct balance between treatments was maintained.

The transfer of supplies was tracked in the central randomization system.

The treatment allocation at the investigator site was performed using a central randomisation system on internet (SBIR). The randomisation algorithm used a minimisation procedure accounting for centre. After having checked the eligibility of the subject, the site staff in charge of the vaccination accessed the randomisation system on internet. Upon providing the subject identification number, the randomisation system used the minimisation algorithm to determine the treatment number to be used for the subject. Each treatment number had to be recorded in the eCRF on the Vaccine Administration screen (Randomisation/Treatment Allocation Section).

Randomisation of subjects to assay subsets

All subjects were to be tested at post-primary vaccination, pre-booster and post-booster time points for the four meningococcal serogroups A, C, W-135 and Y by rSBA. In addition to this, for the other assays and time points, the subjects were randomised so that some assays were performed on subsets:

- At pre-vaccination, 50% of the subjects in the ACWY_3 and ACWY_2 groups were to be tested for rSBA-MenA and rSBA-MenC titres, the other 50% were to be tested for rSBA-MenW-135 and rSBA-MenY titres. In the MenCCRM and MenC-TT groups, 50% of the subjects were to be tested for rSBA-MenC titres and 25% of them were to be tested for rSBA-MenA, rSBA-MenW-135 and rSBA-MenY titres.
- At all time points, 50% of subjects of all groups were to be tested for hSBA titres for each of the four serogroups present in the MenACWY-TT vaccine.
- At all time points, 25% of the subjects of all groups were to be tested for antipneumococcal antibody concentrations by ELISA assay. The other 25% were to be tested for antibody concentrations/titres against the antigens present in the DTPa-IPV-HBV/Hib vaccine.

Subjects in each group were randomly allocated to Subset 1, 2, 3, 4, 5 and 6, as shown:

Group	Subset 1	Subset 2	Subset 3	Subset 4	Subset 5	Subset 6
ACWY_3	25%	25%	25%	25%	-	-
ACWY_2	25%	25%	25%	25%	-	-
MenCCRM	25%	25%	-	-	25%	25%
MenC-TT	25%	25%	-	-	25%	25%

- **Subset 1:**
  - rSBA-MenAC at pre-vaccination
  - hSBA-MenAC at all time points
- **Subset 2:**
  - rSBA-MenWY at pre-vaccination
  - hSBA-MenWY at all time points
- **Subset 3:**
  - rSBA-MenAC at pre-vaccination
  - hSBA-MenAC at all time points
  - 10 pneumococcal serotypes at all time points.
- **Subset 4:**
  - rSBA-MenWY at pre-vaccination
  - hSBA-MenWY at all time points
  - Anti-TT, anti-D, anti-FHA, anti-PT, anti-PRN, anti-HBs, anti-PRP and anti-polio 1, 2, 3 at all time points
- **Subset 5:**
  - rSBA-MenC at pre-vaccination
  - hSBA-MenAC at all time points
  - 10 pneumococcal serotypes at all time points.
- **Subset 6:**
  - hSBA-MenWY at all time points
  - Anti-TT, anti-D, anti-FHA, anti-PT, anti-PRN, anti-HBs, anti-PRP and anti-polio 1, 2, 3 at all time points.

- **Blinding (masking)**

This was an open study. A double-blinded design was not feasible due to differences in the presentation of the study vaccines and vaccination schedules across the study groups.
Although this was an open-label study, the laboratory in charge of the laboratory testing was blinded to the treatment, and codes were used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.
The serological data, which would lead to the unblinding of the treatment groups, were not available during the course of the study to any investigator or any person involved in the clinical conduct of the study (including data cleaning).

CHMP comment: The hierarchical testing strategy is appropriate.
In theory, the Applicant should have pre-specified both the ATP cohort and the primary total vaccinated cohort as co-primary in this non-inferiority study. In practice, both were analysed and reached the same conclusion (See Results, below).

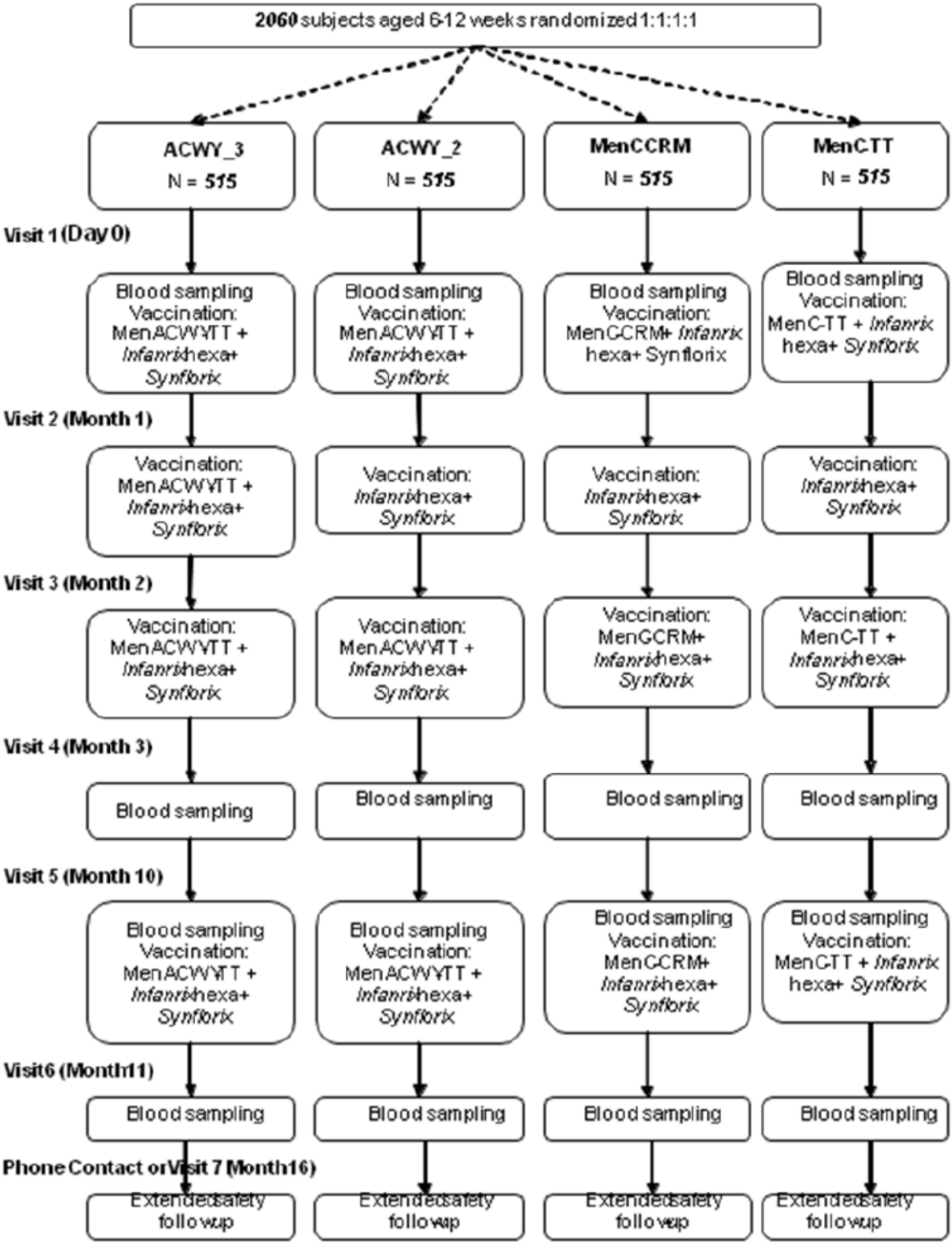
All CIs computed were two-sided 95% CI.

The exact 95% CIs for a proportion within a group were calculated based on the method by Clopper [Clopper, 1934]. The standardised asymptotic 95% CI for the group difference in proportions were based on the method 6 described in paper by Newcombe [Newcombe, 1998]. The 95% CIs for GMTs/GMCs were obtained within each group separately. The 95% CI for the mean of log-transformed titre/concentration was first obtained assuming that log-transformed values were normally distributed with unknown variance. The 95% CI for the GMTs/GMCs were then obtained by exponential transformation of the 95% CI for the mean of log-transformed titre/concentration.

CHMP comment: The statistical methods are acceptable.

Results

- **Participant flow**



The intervals between study visits are provided in Table 4:

Table 4 Intervals between study visits

Interval	Optimal length of interval [1]	Maximum interval allowed
DoB → Visit 1	60 days	42 – 90 days [2]
Visit 1 → Visit 2	30 days	21 - 48 days [2]
Visit 2 → Visit 3	30 days	21 - 48 days [2]
Visit 3 → Visit 4	30 days	21 -48 days [2]
DoB →Visit 5 [3]	12 months	12-13 months [2,3]
Visit 5 → Visit 6	30 days	21 - 48 days [2]
Visit 5 → Phone Contact or Visit 7	180 days	180 - 210 days

[1] Whenever possible the investigator had to arrange study visits within this interval.
[2] Subjects were not eligible for inclusion in the cohort for analysis if they made the study visit outside this interval.
[3] DoB (Date of Birth) to Visit 5: at least 12 months and at the latest on the day before the 14th month birthday of the subject.
If a subject returned for the Visit 4 and/or Visit 6 blood draw prior to completion of the 31-day safety follow-up period, the subject was instructed to continue to record this information on the diary card until 31 days post-vaccination and mail the diary card to the site. The investigator was instructed to make an attempt to obtain this information as soon as possible after the 31-day follow-up period if it was not mailed in.

- **Conduct of the study**

Protocol amendments

There were 3 amendments to the original protocol dated 27 January 2010.

1. Amendment 1 (06 December 2010): administrative changes
2. Amendment 2 (25 May 2011): the sample size of the study population was increased by about 50% to overcome variability in laboratory results for SBA testing; to support the data obtained by rSBA testing, hSBA testing was also performed; assays for streptococcus pneumoniae opsonophagocytotic activity and antibodies to meningococcal PS were removed based on WHO advice.
3. Amendment 3 (30 July 2012): to allow administration of MMR or MMRV vaccine throughout the study in line with local governmental recommendations to address a measles outbreak in Spain.

The statistical analysis plan was revised to cater for changes in laboratory testing.

CHMP comment: the amendments are noted without further comment.

Protocol Deviations leading to elimination from ATP analyses are presented in Table 23:

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Table 23 **Number of subjects enrolled into the study as well as the number of subjects excluded from ATP analyses for the primary epoch with reasons for exclusion**

	Total			ACWY_3		ACWY_2		MenCCRM		MenC-TT	
Title	n	s	%	n	s	n	s	n	s	n	s
Total Enrolled cohort	2095			528		524		516		527	
Primary Total Vaccinated cohort	2095		100	528		524		516		527	
Administration of vaccine(s) forbidden in the protocol (code 1040)	1	1		1	1	0	0	0	0	0	0
Randomisation failure (code 1050)	3	3		0	0	2	2	1	1	0	0
Study vaccine dose not administered according to protocol (code 1070)	4	4		0	0	2	2	1	1	1	1
Vaccine temperature deviation (code 1080)	12	12		3	3	3	3	3	3	3	3
Ineligible subjects as per age window and eligibility criteria (code 1500)	16	17		4	5	2	2	4	4	6	6
RDE Data not signed by the investigator (code 1700)	2	2		0	0	1	1	0	0	1	1
Randomization done in SBIR before the ICF is signed (code 1800)	3	3		1	1	0	0	1	1	1	1
Primary ATP cohort for safety	2054		98.0	519		514		506		515	
Administration of any medication forbidden by the protocol (code 2040)	11	11		2	2	6	6	1	1	2	2
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	39	41		10	10	11	12	10	10	8	9
Non compliance with blood sampling schedule (including wrong and unknown dates (code 2090)	23	25		5	6	6	7	6	6	6	6
Essential serological data missing (code 2100)	140	148		37	41	33	34	30	31	40	42
Primary ATP cohort for immunogenicity	1841		87.9	465		458		459		459	

ACWY_3 = Subjects who received 3 primary doses of MenACWY-TT at 2, 3 and 4 months of age
ACWY_2 = Subjects who received 2 primary doses of MenACWY-TT at 2 and 4 months of age
MenCCRM = Subjects who received 2 primary doses of *Menjugate* at 2 and 4 months of age
MenC-TT = Subjects who received 2 primary doses of *NeisVac-C* at 2 and 4 months of age
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Primary Total Vaccinated cohort

CHMP comment: the protocol deviations appear to be balanced across the 4 groups. It is considered that the nature and number of deviations would not give rise to any cause for concern over study value.

Withdrawals

The number of subjects vaccinated, completed and withdrawn and reason for withdrawal is presented in the following table:

Table 21 **Number of subjects vaccinated, completed and withdrawn with reason for withdrawal - primary epoch (Primary Total Vaccinated cohort)**

	ACWY_3	ACWY_2	MenCCRM	MenC-TT	Total
Number of subjects vaccinated in Primary epoch	528	524	516	527	2095
Number of subjects completed Primary epoch	508	517	508	509	2042
Number of subjects withdrawn during Primary epoch	20	7	8	18	53
Reasons for withdrawal :					
Serious Adverse Event	2	0	1	0	3
Non-Serious Adverse Event	1	0	0	1	2
Protocol violation	2	0	1	0	3
Consent withdrawal (not due to an adverse event)	9	5	3	10	27
Migrated/moved from study area	4	1	2	3	10
Lost to follow-up (subjects with incomplete vaccination course)	2	0	1	2	5
Lost to follow-up (subjects with complete vaccination course)	0	0	0	0	0
Sponsor study termination	0	0	0	0	0
Others	0	1	0	2	3

ACWY_3 = Subjects who received 3 primary doses of MenACWY-TT at 2, 3 and 4 months of age
ACWY_2 = Subjects who received 2 primary doses of MenACWY-TT at 2 and 4 months of age
MenCCRM = Subjects who received 2 primary doses of *Menjugate* at 2 and 4 months of age
MenC-TT = Subjects who received 2 primary doses of *NeisVac-C* at 2 and 4 months of age
Vaccinated = number of subjects who received at least one vaccine dose in the Primary epoch
Completed = number of subjects who completed Visit 4
Withdrawn = number of subjects who did not come for Visit 4

Of the 2095 subjects in the Primary Total Vaccinated Cohort, 2042 subjects completed the primary epoch. The main reason for consent withdrawal was; not due to an adverse event, followed by migration from the study area or loss to follow-up.

CHMP comment: withdrawals and reasons are noted without further comment.

Efficacy results

- **Outcomes and estimation**

The first confirmatory primary objective of the study was met as non inferiority of the 3-dose schedule of MenACWY-TT conjugate vaccine versus the 2-dose schedule of MenC-CRM197 conjugate vaccine was demonstrated, since the lower confidence interval limit in the percentage of subjects with post-primary vaccination rSBAMenC titres ≥ 1:8 for ACWY_3 group minus MenCCRM group is above -5% (- 1.17%) (Table 41):

Table 41 Difference between groups (ACWY_3 minus MenCCRM) in percentage of subjects with rSBA-MenC titre equal to or above 1:8 and 1:128, at one month post-primary vaccinations (Primary ATP cohort for immunogenicity)

								Difference in percentage (ACWY_3 minus MenCCRM)		
		ACWY_3			MenCCRM				95% CI	
Antibody	Type	N	n	%	N	n	%	%	LL	UL
rSBA-MenC	1:8	461	459	99.6	455	453	99.6	0.01	-1.17	1.20
	1:128	461	425	92.2	455	437	96.0	-3.85	-7.05	-0.83

ACWY_3 = Subjects who received 3 primary doses of MenACWY-TT at 2, 3 and 4 months of age
MenCCRM = Subjects who received 2 primary doses of *Menjugate* at 2 and 4 months of age
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit

The second confirmatory primary objective of the study was met as non inferiority of the 3-dose schedule of MenACWY-TT conjugate vaccine versus the 2-dose schedule of MenC-TT conjugate vaccine was demonstrated, since the lower confidence interval limit in the percentage of subjects with post-primary vaccination rSBAMenC titres ≥ 1:8 for ACWY_3 group minus MenC-TT group is above -5% (- 1.57%) (Table 42):

Table 42 Difference between groups (ACWY_3 minus MenC-TT) in percentage of subjects with rSBA-MenC titre equal to or above 1:8 and 1:128, at one month post-primary vaccinations (Primary ATP cohort for immunogenicity)

								Difference in percentage (ACWY_3 minus MenC-TT)		
		ACWY_3			MenC-TT				95% CI	
Antibody	Type	N	n	%	N	n	%	%	LL	UL
rSBA-MenC	1:8	461	459	99.6	457	457	100	-0.43	-1.57	0.40
	1:128	461	425	92.2	457	456	99.8	-7.59	-10.43	-5.40

ACWY_3 = Subjects who received 3 primary doses of MenACWY-TT at 2, 3 and 4 months of age
MenC-TT = Subjects who received 2 primary doses of *NeisVac-C* at 2 and 4 months of age
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit

The third confirmatory primary objective of the study was met as the immunogenicity of the 3-dose schedule for MenACWY-TT for serogroups A, W-135 and Y was demonstrated, since the lower confidence interval limit of subjects with post-primary vaccination rSBA antibody titres ≥ 1:8 in the ACWY_3 group is greater than 80% for each serogroup (98.1%, 97.8% and 90.3%) (Table 43):

Table 43 Number and percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY antibody titre equal to or above 1:8 and 1:128 and GMTs (Primary ATP cohort for immunogenicity)

				≥ 1:8				≥ 1:128				GMT		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
rSBA-MenA	ACWY_3	PRE	223	2	0.9	0.1	3.2	1	0.4	0.0	2.5	4.1	4.0	4.2
		PIII(M3)	462	459	99.4	98.1	99.9	402	87.0	83.6	89.9	250.7	228.6	274.8
	ACWY_2	PRE	219	4	1.8	0.5	4.6	0	0.0	0.0	1.7	4.1	4.0	4.2
		PIII(M3)	456	444	97.4	95.4	98.6	374	82.0	78.2	85.4	203.5	182.0	227.5
	MenCCRM	PRE	97	2	2.1	0.3	7.3	0	0.0	0.0	3.7	4.1	4.0	4.3
		PIII(M3)	455	6	1.3	0.5	2.8	3	0.7	0.1	1.9	4.1	4.0	4.3
	MenC-TT	PRE	110	2	1.8	0.2	6.4	0	0.0	0.0	3.3	4.1	3.9	4.3
		PIII(M3)	457	3	0.7	0.1	1.9	1	0.2	0.0	1.2	4.1	4.0	4.2
rSBA-MenC	ACWY_3	PRE	223	12	5.4	2.8	9.2	2	0.9	0.1	3.2	4.4	4.1	4.8
		PIII(M3)	461	459	99.6	98.4	99.9	425	92.2	89.4	94.5	397.7	358.5	441.2
	ACWY_2	PRE	220	10	4.5	2.2	8.2	1	0.5	0.0	2.5	4.3	4.1	4.5
		PIII(M3)	456	450	98.7	97.2	99.5	428	93.9	91.2	95.9	611.7	539.9	692.9
	MenCCRM	PRE	207	15	7.2	4.1	11.7	6	2.9	1.1	6.2	4.9	4.4	5.5
		PIII(M3)	455	453	99.6	98.4	99.9	437	96.0	93.8	97.6	957.6	850.2	1078.6
	MenC-TT	PRE	220	14	6.4	3.5	10.4	5	2.3	0.7	5.2	4.7	4.3	5.2
		PIII(M3)	457	457	100	99.2	100	456	99.8	98.8	100	1188.1	1080.4	1306.6
rSBA-MenW-135	ACWY_3	PRE	215	8	3.7	1.6	7.2	0	0.0	0.0	1.7	4.3	4.1	4.5
		PIII(M3)	461	457	99.1	97.8	99.8	434	94.1	91.6	96.1	1120.7	977.9	1284.4
	ACWY_2	PRE	217	12	5.5	2.9	9.5	1	0.5	0.0	2.5	4.4	4.1	4.6
		PIII(M3)	455	451	99.1	97.8	99.8	435	95.6	93.3	97.3	1605.0	1383.2	1862.3
	MenCCRM	PRE	110	5	4.5	1.5	10.3	1	0.9	0.0	5.0	4.3	3.9	4.8
		PIII(M3)	453	9	2.0	0.9	3.7	8	1.8	0.8	3.4	4.4	4.1	4.7
	MenC-TT	PRE	107	3	2.8	0.6	8.0	1	0.9	0.0	5.1	4.3	3.9	4.7
		PIII(M3)	455	8	1.8	0.8	3.4	4	0.9	0.2	2.2	4.2	4.0	4.5
rSBA-MenY	ACWY_3	PRE	215	6	2.8	1.0	6.0	0	0.0	0.0	1.7	4.2	4.0	4.4
		PIII(M3)	461	429	93.1	90.3	95.2	371	80.5	76.6	84.0	264.6	224.6	311.7
	ACWY_2	PRE	219	6	2.7	1.0	5.9	3	1.4	0.3	4.0	4.2	4.0	4.5
		PIII(M3)	456	448	98.2	96.6	99.2	407	89.3	86.0	91.9	483.3	418.6	558.0
	MenCCRM	PRE	111	8	7.2	3.2	13.7	1	0.9	0.0	4.9	4.7	4.2	5.2
		PIII(M3)	455	11	2.4	1.2	4.3	9	2.0	0.9	3.7	4.4	4.1	4.6
	MenC-TT	PRE	107	3	2.8	0.6	8.0	1	0.9	0.0	5.1	4.2	3.9	4.6
		PIII(M3)	457	14	3.1	1.7	5.1	13	2.8	1.5	4.8	4.5	4.2	4.8

ACWY_3 = Subjects who received 3 primary doses of MenACWY-TT at 2, 3 and 4 months of age
ACWY_2 = Subjects who received 2 primary doses of MenACWY-TT at 2 and 4 months of age
MenCCRM = Subjects who received 2 primary doses of *Menjugate* at 2 and 4 months of age
MenC-TT = Subjects who received 2 primary doses of *NeisVac-C* at 2 and 4 months of age
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Pre-primary vaccination at Month 0
PIII(M3) = Post primary vaccination at Month 3

[The sixth confirmatory primary objective of the study was met as the immunogenicity of the 2-dose schedule for MenACWY-TT for serogroups A, W-135 and Y was demonstrated, since the lower confidence interval limit of subjects with post-primary vaccination rSBA antibody titres ≥ 1:8 in the ACWY_2 group is greater than 80% for each serogroup (95.4%, 97.8% and 96.6%) (Table 43, above)]

The fourth confirmatory primary objective of the study was met as non inferiority of the 2-dose schedule of MenACWY-TT conjugate vaccine versus the 2-dose schedule of MenC-CRM197 conjugate vaccine was demonstrated, since the lower confidence interval limit in the percentage of subjects with post-primary vaccination rSBAMenC titres ≥ 1:8 for ACWY_2 group minus MenCCRM group is above -5% (- 2.45%) (Table 44):

Table 44 **Difference between groups (ACWY_2 minus MenCCRM) in percentage of subjects with rSBA-MenC titre equal to or above 1:8 and 1:128, at one month post-primary vaccinations (Primary ATP cohort for immunogenicity)**

								Difference in percentage (ACWY_2 minus MenCCRM)		
		ACWY_2			MenCCRM				95% CI	
Antibody	Type	N	n	%	N	n	%	%	LL	UL
rSBA-MenC	1:8	456	450	98.7	455	453	99.6	-0.88	-2.45	0.43
	1:128	456	428	93.9	455	437	96.0	-2.18	-5.18	0.68

ACWY_2 = Subjects who received 2 primary doses of MenACWY-TT at 2 and 4 months of age
MenCCRM = Subjects who received 2 primary doses of *Menjugate* at 2 and 4 months of age
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit

The fifth confirmatory primary objective of the study was met as non inferiority of the 2-dose schedule of MenACWY-TT conjugate vaccine versus the 2-dose schedule of MenC-TT conjugate vaccine was demonstrated, since the lower confidence interval limit in the percentage of subjects with post-primary vaccination rSBAMenC titres ≥ 1:8 for ACWY_2 group minus MenC-TT group is above -5% (- 2.84%) (Table 45):

Table 45 **Difference between groups (ACWY_2 minus MenC-TT) in percentage of subjects with rSBA-MenC titre equal to or above 1:8 and 1:128, at one month post-primary vaccinations (Primary ATP cohort for immunogenicity)**

								Difference in percentage (ACWY_2 minus MenC-TT)		
		ACWY_2			MenC-TT				95% CI	
Antibody	Type	N	n	%	N	n	%	%	LL	UL
rSBA-MenC	1:8	456	450	98.7	457	457	100	-1.32	-2.84	-0.48
	1:128	456	428	93.9	457	456	99.8	-5.92	-8.54	-3.96

ACWY_2 = Subjects who received 2 primary doses of MenACWY-TT at 2 and 4 months of age
MenC-TT = Subjects who received 2 primary doses of *NeisVac-C* at 2 and 4 months of age
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit

CHMP comment: efficacy results are noted without further comment.

Additional comments on primary objectives by assessor of statistics:

Results for primary epoch
Difference between groups in percentage of subjects with rSBA-MenC titre equal to or above 1:8 at one month post-primary vaccinations (Objectives 1, 2, 4 and 5)

							Difference in percentage		
	N	n	%	N	n	%		95% CI	
	3 dose MenACWY-TT			2 dose MenC-CRM197			%	LL	UL
ATP	461	459	99.6	455	453	99.6	0.01	-1.17	1.2
TV	483	481	99.6	481	479	99.6	0	-1.12	1.13
	3 dose MenACWY-TT			2 dose MenC-TT					
ATP	461	459	99.6	457	457	100	-0.43	-1.57	0.4
TV	483	481	99.6	483	483	100	-0.41	-1.5	0.38
	2 dose MenACWY-TT			2 dose MenC-CRM197					
ATP	456	450	98.7	455	453	99.6	-0.88	-2.45	0.43
TV	488	480	98.4	481	479	99.6	-1.22	-2.84	0.06
	MenACWY-TT			2 dose MenC-TT					
ATP	456	450	98.7	457	457	100	-1.32	-2.84	-0.48
TV	488	480	98.4	483	483	100	-1.64	-3.2	-0.83

CHMP comment: The six co-primary objectives were met in the ATP and total vaccinated cohorts.

Secondary objectives

At one month post-primary vaccination the responses were:

rSBA:

rSBA titres ≥ 1:128 and GMTs for the ACWY_3 and ACWY_2 groups:

• The percentage of subjects with rSBA titers ≥ 1:128 in the ACWY_3 group ranged from 80.5% (rSBA-MenY) to 94.1% (rSBA-MenW-135).

• The percentage of subjects with rSBA titers ≥ 1:128 in the ACWY_2 group ranged from 82.0% (rSBA-MenA) to 95.6% (rSBA-MenW-135).

GMTs ranged from 250.7 for rSBA-MenA to 1120.7 for rSBA-MenW-135 in the ACWY_3 group.
GMTs ranged from 203.5 for rSBA-MenA to 1605.0 for rSBA-MenW-135 in the ACWY_2 group.

rSBA-Men C titres ≥ 1:8 and ≥ 1:128 and GMTs for the MenCCRM and MenC-TT groups:

• The percentage of subjects with rSBA-MenC titers ≥ 1:8 and ≥ 1:128 was 99.6% and 96.0%, respectively, in the MenCCRM group and 100% and 99.8%, respectively, in the MenC-TT group. GMTs were 957.6 in the MenCCRM group and 1188.1 in the MenC-TT group.

hSBA:

hSBA titres ≥ 1:8 and GMTs for the ACWY_3 and ACWY_2 groups:
• The percentage of subjects with hSBA titers ≥ 1:8 in the ACWY_3 group ranged from 88.5% (hSBA-MenY) to 99.5% (hSBA-MenC).
• The percentage of subjects with hSBA titers ≥ 1:8 in the ACWY_2 group ranged from 96.5% (hSBA-MenA) to 100% (hSBA-MenW-135).

GMTs ranged from 66.5 for hSBA-MenY to 765.6 for hSBA-MenC in the ACWY_3 group.
GMTs ranged from 157.2 for hSBA-MenA to 1308.3 for hSBA-MenC in the ACWY_2 group.

hSBA-MenC titres ≥ 1:8 and GMTs for the MenCCRM and MenC-TT groups:
• The percentage of subjects with hSBA-MenC titers ≥ 1:8 was 100% for both the MenCCRM and the MenC-TT groups.

GMTs were 2626.5 in the MenC-TT group and 3188.1 in the MenCCRM group.

Infanrix Hexa:

Anti-D:
The percentage of subjects with anti-D concentrations ≥ 0.1 IU/ml was 100% for all four vaccine groups. The percentage of subjects with anti-D concentrations ≥ 1.0 IU/ml ranged from 84.6% for the ACWY_3 group to 94.3% for the MenCCRM group.

GMCs ranged from 2.171 IU/ml in the ACWY_3 group to 3.005 IU/ml in the MenCCRM group.

Anti-TT:
The percentage of subjects with anti-TT concentrations ≥ 0.1 IU/ml was 100% for all four vaccine groups. The percentage of subjects with anti-TT concentrations ≥ 1.0 IU/ml ranged from 95.6% for the ACWY_2 group to 99.1% for the MenC-TT group.

GMCs ranged from 2.847 IU/ml in the MenCCRM group to 4.339 IU/ml in the MenC-TT group.

Anti-PT, FHA and PRN:
All subjects in all four groups had anti-PT, anti-FHA and anti-PRN antibody concentrations ≥5 EL.U/ml.

GMCs ranged from 52.7 EL.U/ml for PT in the ACWY_3 group to 149.2 EL.U/ml for FHA in the ACWY_2 group.

Anti-PT, FHA and PRN vaccine response:

• Vaccine response to the pertussis antigens ranged from 82.4% for FHA in the MenC-TT group to 95.5% for PT in the MenCCRM group.

Anti-HBs:

The percentage of subjects with anti-HBs concentrations ≥ 10.0 mIU/ml was 98.8% for the ACWY_3 and MenC-TT groups and 100% for the ACWY_2 and MenCCRM groups.
The percentage of subjects with anti-HBs concentrations ≥ 100 mIU/ml ranged from 86.0% for the ACWY_3 group to 94.7% for the MenCCRM group.

GMCs ranged from 692.3 mIU/ml in the ACWY_3 group to 848.3 mIU/ml in the MenCCRM group.

Anti-PRP:

The percentage of subjects with anti-PRP concentrations ≥ 0.15 μg/ml ranged from 98.4% (MenCCRM group) to 100% (ACWY_3 and ACWY_2 groups). The percentage of subjects with anti-PRP concentrations ≥ 1.0 μg/ml ranged from 76.4% (MenCCRM group) to 93.0% (MenC-TT group).

GMCs ranged from 2.752 µg/ml in the MenCCRM group to 4.662 µg/ml in the MenC-TT group.

Synflorix:

Pneumococcal antigens:

One month following the primary vaccination, the percentage of subjects with pneumococcal antibody concentrations ≥ 0.35 μg/mL was at least 74.0% for all groups and all serotypes.

GMCs ranged from 0.7 µg/ml for serotype 5 in the ACWY_2 group to 8.51 µg/ml for serotype 14 in the MenCCRM group.

Booster phase

At one month post-booster vaccination responses were:

rSBA:

rSBA titres ≥1:8 and ≥ 1:128 and GMTs for the ACWY_3 and ACWY_2 groups:

The percentage of subjects with rSBA titers ≥ 1:8 and ≥ 1:128 post-booster in the ACWY_3 and ACWY_2 groups was at least than 99.1% and 95.4%, respectively, for all serogroups.

GMTs ranged from 630.6 for rSBA-MenY to 1955.9 for rSBA-MenW-135 in the ACWY_3 group.
GMTs ranged from 881.3 for rSBA-MenY to 2777.2 for rSBA-MenW-135 in the ACWY_2 group.

rSBA-Men C titres ≥ 1:8 and ≥ 1:128 and GMTs for the MenCCRM and MenC-TT groups:

The percentage of subjects with rSBA-MenC titers ≥ 1:8 and ≥ 1:128 post-booster was 98.4% and 95.5%, respectively, in the MenCCRM group and 100% and 99.6%, respectively, in the MenC-TT group.

GMTs ranged from 1051.4 in the MenCCRM group to 1960.2 in the MenC-TT group.

hSBA:

hSBA titres ≥ 1:8 and GMTs for the ACWY_3 and ACWY_2 groups:

The percentage of subjects with hSBA titers ≥ 1:8 in the ACWY_3 and ACWY_2 group was greater than 99.0% for all serogroups.

GMTs ranged from 1192.7 for hSBA-MenA to 4411.2 for hSBA-MenC in the ACWY_3 group.
GMTs ranged from 1007.2 for hSBA-MenA to 5122.7 for hSBA-MenW-135 in the ACWY_2 group.

hSBA-Men C titres ≥ 1:8 and GMTs for the MenCCRM and MenC-TT groups:

The percentage of subjects with hSBA-MenC titers ≥ 1:8 post-booster was 100% in both the MenCCRM and MenC-TT groups.
GMTs were 5438.2 in the MenCCRM group and 5542.3 in the MenC-TT group.

Infanrix Hexa:

Anti-D:

The percentage of subjects with anti-D concentrations post-booster ≥ 0.1 IU/ml was 100% for all four vaccine groups. The percentage of subjects with anti-D concentrations ≥ 1.0 IU/ml ranged from 94.6% for the ACWY_2 group to 100% for the MenCCRM group.

GMCs ranged from 5.032 IU/ml in the ACWY_3 group to 9.078 IU/ml in the MenCCRM group.

Anti-TT:

The percentage of subjects with anti-TT concentrations post-booster ≥ 0.1 IU/ml was 100% for all four vaccine groups. The percentage of subjects with anti-TT concentrations ≥ 1.0 IU/ml was from 99.2% for the MenCCRM group and 100% for the other three vaccine groups.

GMCs ranged from 8.400 IU/ml in the MenCCRM group to 13.016 IU/ml in the MenC-TT group.

Anti-PT, FHA and PRN:

All subjects in all four groups had anti-PT, anti-FHA and anti-PRN antibody concentrations ≥5 EL.U/ml.

GMCs ranged from 78.2 EL.U/ml. for PT in the ACWY_2 group to 334.3 EL.U/ml. for PRN in the MenC-TT group.

Anti-PT, FHA and PRN booster response:

• Booster response to the pertussis antigens ranged from 92.2% for PT in the MenCCRM group to 100% for PRN in the ACWY_2 group.

Anti-HBs:

The percentage of subjects with anti-HBs concentrations ≥ 10.0 mIU/ml was 97.9% for the ACWY_3 and 100% for the ACWY_2 and MenCCRM and MenC-TT groups.
The percentage of subjects with anti-HBs concentrations post-booster ≥ 100 mIU/ml ranged from 95.9% for the ACWY_3 group to 100% for the ACWY_2 group.

GMCs ranged from 3624.9 mIU/ml in the ACWY_3 group to 4866.4 mIU/ml in the MenCCRM group.

Anti-PRP:

All subjects in all four groups had anti-PRP concentrations ≥ 0.15 μg/ml. The percentage of subjects with anti-PRP concentrations ≥ 1.0 μg/ml ranged from 96.6% for the MenC-TT group to 100% for the ACWY_2 and MenCCRM groups.

GMCs ranged from 17.350 µg/ml in the ACWY_3 group to 23.973 µg/ml in the MenC-TT group.

Synflorix:

Pneumococcal antigens:

• One month following the booster vaccination, the percentage of subjects with pneumococcal antibody concentrations ≥ 0.35 μg/mL was at least 91.1% for all groups and all serotypes.

GMCs ranged from 0.84 µg/ml for serotype 5 in the MenC-TT group to 9.75 µg/ml for serotype 14 in the MenCCRM group.

CHMP comment: efficacy results are noted without further comment.

Safety results

Introduction

All AEs (solicited and unsolicited) starting following administration of each dose of study vaccine/comparator were recorded.

AEs of specific interest for safety monitoring included new onset of chronic illness(es) (e.g. autoimmune disorders, asthma, type I diabetes and allergies).

Occurrences of AEs of specific interest were to be reported up to six months post-booster dose, whether or not they were considered to be possibly related to the treatment administration.

The intensity of each AE and SAE recorded in the eCRF or SAE Report screens, as applicable, was to be assigned to one of the following categories:

1 (mild)	=	An AE which was easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which was sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevented normal, everyday activities (in a young child, such an AE would, for example, have prevented attendance at school/kindergarten/a day-care centre and would have caused the parent(s)/LAR(s) to seek medical advice).

The following local (injection-site) AEs were solicited:

Table 10 Solicited local adverse events

Pain at injection site
Redness at injection site
Swelling at injection site

The following general AEs were solicited:

Table 11 Solicited general adverse events

Drowsiness
Fever
Irritability/Fussiness
Loss of appetite

As a consistent method of soliciting AEs, the subject's parent(s)/LAR(s) were asked a non-leading question such as: '*Has your child acted differently or felt different in any way since receiving the vaccine or since the last visit*?'

An 8-day follow-up (Day 0 to Day 7) of solicited AEs was to be performed after each vaccination.

The intensity of the solicited AEs was to be assessed as described in Table 12:

Table 12 Intensity scales for solicited symptoms

Infant/Toddler (15–24 months)/Child (< 6 years)		
Adverse Event	**Intensity grade**	**Parameter**
Pain at injection site	0	None
	1	Mild: Minor reaction to touch
	2	Moderate: Cried/protested on touch
	3	Severe: Cried when limb was moved/spontaneously painful
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever*		Record temperature in °C/°F
Irritability/Fussiness	0	Behaviour as usual
	1	Mild: Crying more than usual/no effect on normal activity
	2	Moderate: Crying more than usual/interfered with normal activity
	3	Severe: Crying that could not be comforted/prevented normal activity
Drowsiness	0	Behaviour as usual
	1	Mild: Drowsiness easily tolerated
	2	Moderate: Drowsiness that interfered with normal activity
	3	Severe: Drowsiness that prevented normal activity
Loss of appetite	0	Appetite as usual
	1	Mild: Eating less than usual/no effect on normal activity
	2	Moderate: Eating less than usual/interfered with normal activity
	3	Severe: Not eating at all

*Fever was defined as: rectal temperature ≥38°C / axillary temperature ≥37.5°C /oral temperature ≥37.5°C/ tympanic temperature on oral setting ≥37.5°C / tympanic temperature on rectal setting ≥38°C
The preferred route for recording temperature in this study was rectal.

The maximum intensity of local injection site redness/swelling was scored at GSK Biologicals as follows:

0 : None
1* : > 0 - ≤ 10 mm
2 : > 10 mm - ≤ 30 mm
3 : > 30 mm

*Note: Grade 1 redness and swelling measurement has been changed to ≥0.1 - ≤ 10 mm. Subjects who reported redness and swelling with measurement <0.1 mm were considered as subjects without redness or swelling in the analysis.

Assessment of causality

The investigator was obligated to assess the relationship between the investigational product and the occurrence of each AE/SAE. The investigator used clinical judgement to determine the relationship.

All solicited local (injection site) reactions were considered causally related to vaccination. Causality of all other AEs was to be assessed by the investigator using the following question:

Is there a reasonable possibility that the AE may have been caused by the investigational product?

NO : The AE was not causally related to administration of the study vaccine(s). There were other, more likely causes and administration of the study vaccine(s) wa not suspected to have contributed to the AE.

YES : There was a reasonable possibility that the vaccine(s) contributed to the AE.

Outcome of any non-serious AE within 30 days of vaccination was pro-actively assessed and recorded.

Safety analysis is divided in the primary phase and the booster phase.

Primary phase

The analysis of safety was performed on the Primary Total Vaccinated cohort.

Patient exposure

Table 20 Number of subjects by country (Primary Total Vaccinated cohort)

		ACWY_3 N = 528		ACWY_2 N = 524		MenCCRM N = 516		MenC-TT N = 527		Total N = 2095	
Characteristics	Categories	n	%	n	%	n	%	n	%	n	%
Countries	Estonia	9	1.7	8	1.5	8	1.6	9	1.7	34	1.6
	Germany	129	24.4	125	23.9	122	23.6	126	23.9	502	24.0
	Spain	390	73.9	391	74.6	386	74.8	392	74.4	1559	74.4

ACWY_3 = Subjects who received 3 primary doses of MenACWY-TT at 2, 3 and 4 months of age
ACWY_2 = Subjects who received 2 primary doses of MenACWY-TT at 2 and 4 months of age
MenCCRM = Subjects who received 2 primary doses of *Menjugate* at 2 and 4 months of age
MenC-TT = Subjects who received 2 primary doses of *NeisVac-C* at 2 and 4 months of age
N = Number of subjects
n = number of subjects in a given category
% = n / Number of subjects with available results x 100

The number and percentage of subjects who received a vaccine dose is presented in Table 361:

Table 361 Number and percentage of subjects who received study vaccine doses by vaccine (Primary Total Vaccinated cohort)

	ACWY_3 MenACWY-TT N = 528		ACWY_3 Infanrix Hexa N = 528		ACWY_3 Synflorix N = 528		ACWY_2* MenACWY-TT N = 524		ACWY_2* Infanrix Hexa N = 524		ACWY_2* Synflorix N = 524		MenCCRM *Menjugate* N = 516		MenCCRM Infanrix Hexa N = 516		MenCCRM Synflorix N = 516		MenC-TT *Neis Vac-C* N = 527		MenC-TT Infanrix Hexa N = 527		MenC-TT Synflorix N = 527	
Total number of doses received	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
1	15	2.8	15	2.8	15	2.8	7	1.3	4	0.8	4	0.8	7	1.4	7	1.4	7	1.4	16	3.0	12	2.3	12	2.3
2	2	0.4	2	0.4	2	0.4	517	98.7	2	0.4	2	0.4	509	98.6	0	0.0	0	0.0	511	97.0	4	0.8	4	0.8
3	511	96.8	511	96.8	511	96.8	0	0.0	518	98.9	518	98.9	0	0.0	509	98.6	509	98.6	0	0.0	511	97.0	511	97.0
Any	528	100	528	100	528	100	524	100	524	100	524	100	516	100	516	100	516	100	527	100	527	100	527	100

ACWY_3 = Subjects who received 3 primary doses of MenACWY-TT at 2, 3 and 4 months of age
ACWY_2 = Subjects who received 2 primary doses of MenACWY-TT at 2 and 4 months of age
MenCCRM = Subjects who received 2 primary doses of *Menjugate* at 2 and 4 months of age
MenC-TT = Subjects who received 2 primary doses of *NeisVac-C* at 2 and 4 months of age
N = number of subjects in each group included in the considered cohort
n/% = number/percentage of subjects receiving the specified total number of doses
Any = number and percentage of subjects receiving at least one dose
Note: PID 1021 in the ACWY_2 group received MenACWY-TT vaccine at Visit 2 instead of Visit 3. As the subject was scheduled to receive the MenACWY-TT vaccine at Visit 3 and not at Visit 2, this vaccination should be considered as concomitant vaccination at Visit 2 and not study vaccination at Visit 3.

Of the total number of subjects vaccinated in the primary phase of the study, 96.8% of subjects in the ACWY_3 group received all 3 doses of MenACWY-TT and the coadminstered vaccines, 98.7% of subjects in the ACWY_2 group received all 2 doses of MenACWY-TT and 98.9% received the co-adminstered vaccines, 98.6% of subjects in the MenCCRM group received all 2 doses of Menjugate and the co-adminstered vaccines and 97.0% of subjects in the MenC-TT group received all 2 doses of NeisVac-C and the co-adminstered vaccines.

Compliance in returning symptom sheets is presented in Table 362:

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Table 362 Compliance in returning symptom sheets (Primary Total Vaccinated cohort)

Dose	Group	Number of doses	Doses NOT according to protocol	Number of general SS	Compliance % general SS	Number of local SS	Compliance % local SS
1	ACWY_3	528	2	518	98.1	518	98.1
	ACWY_2	524	3	523	99.8	523	99.8
	MenCCRM	516	1	508	98.4	509	98.6
	MenC-TT	527	1	517	98.1	517	98.1
2	ACWY_3	513	1	511	99.6	511	99.6
	ACWY_2	520	3	515	99.0	517	99.4
	MenCCRM	509	4	509	100	509	100
	MenC-TT	515	4	512	99.4	513	99.6
3	ACWY_3	511	1	505	98.8	505	98.8
	ACWY_2	518	1	516	99.6	517	99.8
	MenCCRM	509	0	505	99.2	507	99.6
	MenC-TT	511	2	507	99.2	508	99.4
Total	ACWY_3	1552	4	1534	98.8	1534	98.8
	ACWY_2	1562	7	1554	99.5	1557	99.7
	MenCCRM	1534	5	1522	99.2	1525	99.4
	MenC-TT	1553	7	1536	98.9	1538	99.0

ACWY_3 = Subjects who received 3 primary doses of MenACWY-TT at 2, 3 and 4 months of age
ACWY_2 = Subjects who received 2 primary doses of MenACWY-TT at 2 and 4 months of age
MenCCRM = Subjects who received 2 primary doses of *Menjugate* at 2 and 4 months of age
MenC-TT = Subjects who received 2 primary doses of *NeisVac-C* at 2 and 4 months of age
SS = Symptom sheets used for the collection of local and general solicited AEs
Compliance % = (number of doses with symptom sheet return / number of administered doses) X 100

CHMP comment: the high success rate of administration >96% and high compliance in returning symptom sheets >98% add to the credibility of the study reports.

Adverse events

Overall incidence of adverse events

Primary phase

The incidence and nature of symptoms (general v. local) with causal relationship to vaccination are presented in Table 365:

Table 365 Incidence and nature of symptoms (solicited and unsolicited) with causal relationship to vaccination, reported during the 8-day (Days 0-7) post-vaccination period following each dose and overall (Primary Total Vaccinated cohort)

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	ACWY_3	528	426	80.7	77.1	84.0	528	277	52.5	48.1	56.8	528	353	66.9	62.7	70.9
	ACWY_2	524	423	80.7	77.1	84.0	524	276	52.7	48.3	57.0	524	348	66.4	62.2	70.4
	MenCCRM	516	409	79.3	75.5	82.7	516	281	54.5	50.0	58.8	516	344	66.7	62.4	70.7
	MenC-TT	527	427	81.0	77.4	84.3	527	308	58.4	54.1	62.7	527	339	64.3	60.1	68.4
Dose 2	ACWY_3	513	409	79.7	76.0	83.1	513	265	51.7	47.2	56.1	513	348	67.8	63.6	71.9
	ACWY_2	520	417	80.2	76.5	83.5	520	258	49.6	45.2	54.0	520	352	67.7	63.5	71.7
	MenCCRM	509	413	81.1	77.5	84.4	509	260	51.1	46.6	55.5	509	359	70.5	66.4	74.5
	MenC-TT	515	416	80.8	77.1	84.1	515	268	52.0	47.6	56.4	515	356	69.1	64.9	73.1
Dose 3	ACWY_3	511	375	73.4	69.3	77.2	511	225	44.0	39.7	48.5	511	306	59.9	55.5	64.2
	ACWY_2	518	399	77.0	73.2	80.6	518	241	46.5	42.2	50.9	518	328	63.3	59.0	67.5
	MenCCRM	509	385	75.6	71.7	79.3	509	209	41.1	36.8	45.5	509	345	67.8	63.5	71.8
	MenC-TT	511	392	76.7	72.8	80.3	511	231	45.2	40.8	49.6	511	331	64.8	60.5	68.9
Overall/dose	ACWY_3	1552	1210	78.0	75.8	80.0	1552	767	49.4	46.9	51.9	1552	1007	64.9	62.5	67.3
	ACWY_2	1562	1239	79.3	77.2	81.3	1562	775	49.6	47.1	52.1	1562	1028	65.8	63.4	68.2
	MenCCRM	1534	1207	78.7	76.5	80.7	1534	750	48.9	46.4	51.4	1534	1048	68.3	65.9	70.6
	MenC-TT	1553	1235	79.5	77.4	81.5	1553	807	52.0	49.4	54.5	1553	1026	66.1	63.6	68.4
Overall/subject	ACWY_3	528	485	91.9	89.2	94.0	528	370	70.1	66.0	74.0	528	436	82.6	79.1	85.7
	ACWY_2	524	491	93.7	91.3	95.6	524	369	70.4	66.3	74.3	524	443	84.5	81.2	87.5
	MenCCRM	516	478	92.6	90.0	94.7	516	370	71.7	67.6	75.6	516	445	86.2	83.0	89.1
	MenC-TT	527	485	92.0	89.4	94.2	527	386	73.2	69.2	77.0	527	438	83.1	79.6	86.2

ACWY_3 = Subjects who received 3 primary doses of MenACWY-TT at 2, 3 and 4 months of age
ACWY_2 = Subjects who received 2 primary doses of MenACWY-TT at 2 and 4 months of age
MenCCRM = Subjects who received 2 primary doses of *Menjugate* at 2 and 4 months of age
MenC-TT = Subjects who received 2 primary doses of *NeisVac-C* at 2 and 4 months of age
For each dose and overall/subject:
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
For overall/dose:
N = number of administered doses
n/% = number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

During the 8-day follow-up period, at least one symptom (solicited or unsolicited) was reported in 95.6%, 97.5%, 97.1% and 96.2% of subjects in the ACWY_3, ACWY_2, MenCCRM and MenC-TT groups, respectively.

Grade 3 symptoms were reported in 30.7%, 27.9%, 29.8% and 31.3% of subjects in the ACWY_3, ACWY_2, MenCCRM and MenC-TT groups, respectively.

In the ACWY_3 group, 24.1% and 14.2% of subjects reported grade 3 symptoms that were general and local, respectively.
In the ACWY_2 group, 20.6% and 15.8% of subjects reported grade 3 symptoms that were general and local, respectively.
In the MenCCRM group, 21.3% and 16.3% of subjects reported grade 3 symptoms that were general and local, respectively.
In the MenC-TT group, 24.1% and 17.1% of subjects reported grade 3 symptoms that were general and local, respectively.

At least 91.9% of the subjects reported symptoms that were considered by the investigator to be causally related to vaccination in all four groups.

The reporting of symptoms for the 4-day follow-up was similar to the 8-day follow-up. The majority of the symptoms were reported during the 4-day follow-up.

Booster and extended safety follow-up phases

The incidence and nature of symptoms with causal relationship to vaccination are presented in Table 410:

Table 410 Incidence and nature of symptoms (solicited and unsolicited) with causal relationship to vaccination, reported during the 8-day (Days 0-7) post-vaccination period (Booster Total Vaccinated cohort)

	Any symptom					General symptoms					Local symptoms				
				95% CI					95% CI					95% CI	
Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
ACWY_3	497	407	81.9	78.2	85.2	497	252	50.7	46.2	55.2	497	355	71.4	67.2	75.4
ACWY_2	511	411	80.4	76.7	83.8	511	264	51.7	47.2	56.1	511	372	72.8	68.7	76.6
MenCCRM	503	414	82.3	78.7	85.5	503	233	46.3	41.9	50.8	503	369	73.4	69.3	77.2
MenC-TT	506	412	81.4	77.8	84.7	506	255	50.4	45.9	54.8	506	365	72.1	68.0	76.0

ACWY_3 = Subjects who received 3 primary doses of MenACWY-TT at 2, 3 and 4 months of age and 1 booster dose of MenACWY-TT at 12 months of age
ACWY_2 = Subjects who received 2 primary doses of MenACWY-TT at 2 and 4 months of age and 1 booster dose of MenACWY-TT at 12 months of age
MenCCRM = Subjects who received 2 primary doses of *Menjugate* at 2 and 4 months of age and 1 booster dose of *Menjugate* at 12 months of age
MenC-TT = Subjects who received 2 primary doses of *NeisVac-C* at 2 and 4 months of age and 1 booster dose of *NeisVac-C* at 12 months of age
N = number of subjects with the administered dose
n/% = number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

During the 8-day follow-up period, at least one symptom (solicited or unsolicited) was reported in 88.9%, 85.9%, 88.3% and 87.9% of subjects in the ACWY_3, ACWY_2, MenCCRM and MenC-TT groups, respectively.
Grade 3 symptoms were reported in 21.9%, 22.7%, 24.7% and 21.9% of subjects in the ACWY_3, ACWY_2, MenCCRM and MenC-TT groups, respectively.

In the ACWY_3 group, 11.7% and 15.1% of the subjects reported grade 3 symptoms that were general and local, respectively.
In the ACWY_2 group, 11.9% and 14.1% of subjects reported grade 3 symptoms that were general and local, respectively.

In the MenCCRM group, 12.5% and 18.1% of subjects reported grade 3 symptoms that were general and local, respetively.
In the MenC-TT group, 13.0% and 13.4% of subjects reported grade 3 symptoms that were general and local, respectively.

At least 80.4% of the symptoms were considered by the investigator to be causally related to vaccination in all four groups.

Solicited local adverse events

Overall/subject after meningococcal vaccination:

Primary phase

• Redness was the most frequently reported solicited local symptom in all four groups after meningococcal vaccination during the 8-day post-vaccination period (reported by 45.0% of subjects in the ACWY_3 group, 39.4% in the ACWY_2 group, 50.1% in the MenCCRM group and 45.0% in the MenC-TT group).
Grade 3 redness was reported in 0.4% of subjects in the ACWY_3, MenCCRM and MenC-TT groups and 0.2% in the ACWY_2 group.

• Pain was reported in 44.2% of subjects in the ACWY_3 group, 38.6% in the ACWY_2 group, 41.8% in the MenCCRM group and 41.1% in the MenC-TT group during the 8-day post-vaccination period. Grade 3 pain was reported in 5.6% of subjects in the ACWY_3 group, 5.0% in the ACWY_2 group, 3.7% in theMenCCRM group and 6.4% in the MenC-TT group.

• Swelling was reported in in 29.7% of subjects in the ACWY_3 group, 26.0% in the ACWY_2 group, 34.4% in the MenCCRM group and 31.7% in the MenC-TT group during the 8-day post-vaccination period.
Grade 3 swelling was reported in 0.2% of subjects in the ACWY_3 and ACWY_2 groups, 0.6% in the MenCCRM group and 0.8% in the MenC-TT group.

Medical advice was sought by ≤0.4% of subjects for any of the local symptoms in all four groups after meningococcal vaccination.

Booster and ESFU Phases

• Redness was slightly higher than pain as the most frequently reported solicited local symptom in all four groups during the 8-day post-booster vaccination period (reported by 37.9% of subjects in the ACWY_3 group, 43.3% in the ACWY_2 group, 42.9% in the MenCCRM group and 45.3% in the MenC-TT group).
Grade 3 redness was reported in 0.6% of subjects in the ACWY_3 group, 1.2% in the ACWY_2 group, 1.0% in the MenCCRM group and 0.8% in the MenC-TT group.

• Pain was reported in 38.9% of subjects in the ACWY_3 group, 39.8% in the ACWY_2 group, 40.9% in the MenCCRM group and 36.0% in the MenC-TT group during the 8-day post-booster vaccination period.
Grade 3 pain was reported in 4.9% of subjects in the ACWY_3 group, 4.5% in the ACWY_2 group, 6.3% in the MenCCRM group and 3.6% in the MenC-TT group.

• Swelling was reported in in 27.1% of subjects in the ACWY_3 group, 29.8% in the ACWY_2 group, 31.9% in the MenCCRM group and 32.4% in the MenC-TT group during the 8-day post-booster vaccination period.
Grade 3 swelling was reported in 0.2% of subjects in the ACWY_3 group, 0.4% in the ACWY_2 and MenCCRM groups, and 1.0% in the MenC-TT group.

Medical advice was sought by ≤0.2% of subjects for any of the local symptoms in all four groups after meningococcal vaccination.

Solicited general adverse events

Primary phase

• Irritability was the most frequently reported solicited general symptom in all four groups during the 8-day post-vaccination period (80.9% of subjects in the ACWY_3 group, 83.4% in the ACWY_2 group, 86.2% in the MenCCRM group and 85.1% in the MenC-TT group).
Grade 3 irritability was reported in 21.0% of subjects in the ACWY_3 group, 15.9% in the ACWY_2 group, 16.9% in the MenCCRM group and 20.1% in the MenC-TT group.

• Drowsiness was reported in 72.6% of subjects in the ACWY_3 group, 69.8% in the ACWY_2 group, 72.7% in the MenCCRM group and 72.8% in the MenC-TT group during the 8-day post-vaccination period.
Grade 3 drowsiness was reported in 8.7% of subjects in the ACWY_3 group, 7.8% in the ACWY_2 group, 7.9% in the MenCCRM group and 9.1% in the MenC-TT group

• Loss of appetite was reported in 56.9% of subjects in the ACWY_3 group, 62.1% in the ACWY_2 group, 60.3% in the MenCCRM group and 60.2% in the MenC-TT group during the 8-day post-vaccination period.
Grade 3 loss of appetite was reported in 5.4% of subjects in the ACWY_3 group, 4.4% in the ACWY_2 group, 4.3% in the MenCCRM group and 4.2% in the MenC-TT group.

• Temperature was reported in 52.5% of subjects in the ACWY_3 group, 52.4% in the ACWY_2 group, 54.4% in the MenCCRM group and 53.1% in the MenC-TT group during the 8-day post-vaccination period.
Grade 3 temperature was reported in 0.2% of subjects in the ACWY_3 group, 0.4% in the ACWY_2 group, 0.6% in the MenCCRM group and 0.4% in the MenC-TT group.

Medical advice was sought by ≤3.7% of subjects for any of the general symptoms in all four groups. The most frequent symptom for which medical advice was sought was for temperature.

Booster and ESFU Phases

• Irritability was the most frequently reported solicited general symptom in all four groups during the 8-day post-booster vaccination period (reported by 57.8% of subjects in the ACWY_3 group, 58.0% in the ACWY_2 group, 57.3% in the MenCCRM group and 58.9% in the MenC-TT group).
Grade 3 irritability was reported in 8.4% of subjects in the ACWY_3 group, 7.3% in the ACWY_2 group, 7.5% in the MenCCRM group and 8.9% in the MenC-TT group.

• Drowsiness was reported in 40.3% of subjects in the ACWY_3 group, 40.4% in the ACWY_2 group, 41.9% in the MenCCRM group and 40.1% in the MenC-TT group during the 8-day post-booster vaccination period.
Grade 3 drowsiness was reported in 2.9% of subjects in the ACWY_3 group, 2.5% in the ACWY_2 group, 4.2% in the MenCCRM group and 3.6% in the MenC-TT group.

• Loss of appetite was reported in in 38.5% of subjects in the ACWY_3 group, 37.8% in the ACWY_2 group, 39.9% in the MenCCRM group and 38.7% in the MenC-TT group during the 8-day post-booster vaccination period.
Grade 3 loss of appetite was reported in 2.4% of subjects in the ACWY_3 group, 4.1% in the ACWY_2 group, 4.6% in the MenCCRM group and 5.4% in the MenC-TT group.

• Temperature was reported in in 38.1% of subjects in the ACWY_3 group, 35.3% in the ACWY_2 group, 37.5% in the MenCCRM group and 33.7% in the MenC-TT group during the 8-day post-booster vaccination period.
Grade 3 temperature was reported in 0.4% of subjects in the ACWY_3 group, 0.4% in the ACWY_2 group, 0.6% in the MenCCRM group and 1.4% in the MenC-TT group.

Medical advice was sought by ≤2.9% of subjects for any of the general symptoms in all four groups. Medical advice was most frequently sought for temperature.

Unsolicited adverse events

Primary phase

• At least one unsolicited symptom was reported by 55.5 % of subjects in the ACWY_3 group, 52.1% in the ACWY_2 group, 56.4% in the MenCCRM group and 53.1% in the MenC-TT group during the 31-day post-vaccination period.
Grade 3 unsolicited events were reported in 5.3%, 4.0%, 4.8% and 3.2% of subjects in the ACWY_3, ACWY_2, MenCCRM and MenC-TT groups, respectively.
The most frequently reported Grade 3 unsolicited events were bronchiolitis, bronchitis, upper respiratory tract infection and gastroenteritis.

• Unsolicited symptoms considered by the investigator to be causally related during 31-day period post-vaccination were reported in 3.8%, 2.3%, 3.3% and 2.8% of subjects in ACWY_3, ACWY_2, MenCCRM and MenC-TT groups, respectively.

The most common vaccine related symptoms reported were diarrhoea, vomiting and injection site induration.

Booster and ESFU Phases

At least one unsolicited symptom was reported by 36.0 % of subjects in the ACWY_3 group, 36.4% in the ACWY_2 group, 32.6% in the MenCCRM group and 32.8% in the MenC-TT group during the 31-day post-booster vaccination period.
Grade 3 unsolicited events were reported in 2.8%, 3.1%, 3.0% and 3.6% of subjects in the ACWY_3, ACWY_2, MenCCRM and MenC-TT groups, respectively. The most frequently reported Grade 3 unsolicited event was gastroenteritis followed by upper respiratory tract infection.

Unsolicited symptoms considered by the investigator to be causally related during 31-day period post-booster vaccination were reported in 0.8%, 1.0%, 1.0% and 0.8% of subjects in ACWY_3, ACWY_2, MenCCRM and MenC-TT groups, respectively.

The most common vaccine related symptom reported were injection site haematoma and vomiting.

CHMP comment: the overall pattern of adverse symptoms appears similar across all 4 treatment arms.

Serious adverse events and deaths

There were not any fatal events in the primary or booster phases.

Primary phase

The number and percentage of subjects with SAEs classified by MedDRA Primary System Organ Class and Preferred Term reported in the primary phase up to the day preceding the booster dose is presented in Table 381:

Table 381 Percentage of subjects reporting Serious Adverse Events classified by MedDRA Primary System Organ Class and Preferred Term, from first primary vaccine dose up to the day preceding the booster dose (Primary Total Vaccinated cohort)

		ACWY_3 N = 528				ACWY_2 N = 524				MenCCRM N = 516				MenC-TT N = 527			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		43	8.1	6.0	10.8	38	7.3	5.2	9.8	33	6.4	4.4	8.9	37	7.0	5.0	9.5
Blood and lymphatic system disorders (10005329)	Lymphadenitis (10025188)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7
Cardiac disorders (10007541)	Wolff-parkinson-white syndrome (10048015)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7
Congenital, familial and genetic disorders (10010331)	Laryngomalacia (10060786)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Plagiocephaly (10048586)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
Eye disorders (10015919)	Conjunctivitis allergic (10010744)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
Gastrointestinal disorders (10017947)	Aphthous stomatitis (10002958)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Enteritis (10014866)	0	0.0	0.0	0.7	2	0.4	0.0	1.4	1	0.2	0.0	1.1	1	0.2	0.0	1.1
	Gastrooesophageal reflux disease (10017885)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7
	Haematemesis (10018830)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Inguinal hernia (10022016)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7
	Vomiting (10047700)	1	0.2	0.0	1.1	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7
General disorders and administration site conditions (10018065)	Pyrexia (10037660)	0	0.0	0.0	0.7	4	0.8	0.2	1.9	0	0.0	0.0	0.7	2	0.4	0.0	1.4
Immune system disorders (10021428)	Milk allergy (10027633)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
Infections and infestations (10021881)	Abscess (10000269)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7
	Adenovirus infection (10060931)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Atypical pneumonia (10003757)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Bacteraemia (10003997)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Bacterial pyelonephritis (10059517)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7	2	0.4	0.0	1.4
	Bronchiolitis (10006448)	11	2.1	1.0	3.7	10	1.9	0.9	3.5	9	1.7	0.8	3.3	13	2.5	1.3	4.2
	Bronchitis (10006451)	7	1.3	0.5	2.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	6	1.1	0.4	2.5
	Bronchopneumonia (10006469)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	2	0.4	0.0	1.4	0	0.0	0.0	0.7
	Cellulitis (10007882)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Conjunctivitis (10010741)	1	0.2	0.0	1.1	1	0.2	0.0	1.1	1	0.2	0.0	1.1	1	0.2	0.0	1.1
	Conjunctivitis bacterial (10061784)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Croup infectious (10011416)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Epstein-barr virus infection (10015108)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7

		ACWY_3 N = 528				ACWY_2 N = 524				MenCCRM N = 516				MenC-TT N = 527			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Escherichia urinary tract infection (10052238)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Exanthema subitum (10015586)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Gastroenteritis (10017888)	5	0.9	0.3	2.2	3	0.6	0.1	1.7	2	0.4	0.0	1.4	2	0.4	0.0	1.4
	Gastroenteritis bacterial (10061166)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7
	Gastroenteritis norovirus (10068189)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Gastroenteritis rotavirus (10017913)	2	0.4	0.0	1.4	2	0.4	0.0	1.4	1	0.2	0.0	1.1	2	0.4	0.0	1.4
	H1n1 influenza (10069767)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Herpes simplex (10019948)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Influenza (10022000)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Laryngitis (10023874)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Nasopharyngitis (10028810)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Oral candidiasis (10030963)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Osteomyelitis (10031252)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Otitis media (10033078)	2	0.4	0.0	1.4	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Otitis media acute (10033079)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Pertussis (10034738)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Pharyngitis (10034835)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Pneumonia (10035664)	2	0.4	0.0	1.4	1	0.2	0.0	1.1	1	0.2	0.0	1.1	2	0.4	0.0	1.4
	Pneumonia respiratory syncytial viral (10035732)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Pyelonephritis (10037596)	1	0.2	0.0	1.1	1	0.2	0.0	1.1	1	0.2	0.0	1.1	4	0.8	0.2	1.9
	Respiratory syncytial virus bronchiolitis (10038718)	2	0.4	0.0	1.4	3	0.6	0.1	1.7	2	0.4	0.0	1.4	0	0.0	0.0	0.7
	Respiratory syncytial virus infection (10061603)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Rotavirus infection (10067470)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Sepsis (10040047)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Tonsillitis (10044008)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Upper respiratory tract infection (10046306)	3	0.6	0.1	1.7	2	0.4	0.0	1.4	1	0.2	0.0	1.1	0	0.0	0.0	0.7
	Urinary tract infection (10046571)	3	0.6	0.1	1.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7	2	0.4	0.0	1.4
	Viral infection (10047461)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7

113369 (MENACWY-TT-083)
Report Final

		ACWY_3 N = 528				ACWY_2 N = 524				MenCCRM N = 516				MenC-TT N = 527			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Viral rash (10047476)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7
Injury, poisoning and procedural complications (10022117)	Concussion (10010254)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	4	0.8	0.2	2.0	0	0.0	0.0	0.7
	Contusion (10050584)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Joint dislocation (10023204)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7
	Near drowning (10056905)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7
	Overdose (10033295)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
Investigations (10022891)	Alanine aminotransferase increased (10001551)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Aspartate aminotransferase increased (10003481)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Blood alkaline phosphatase increased (10059570)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
Metabolism and nutrition disorders (10027433)	Decreased appetite (10061428)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
Musculoskeletal and connective tissue disorders (10028395)	Muscle spasms (10028334)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	Cerebral haemangioma (10048788)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
Nervous system disorders (10029205)	Epilepsy (10015037)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	1	0.2	0.0	1.1	1	0.2	0.0	1.1
	Febrile convulsion (10016284)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Hypotonia (10021118)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7
Psychiatric disorders (10037175)	Breath holding (10006322)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
Renal and urinary disorders (10038359)	Haematuria (10018867)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7
Respiratory, thoracic and mediastinal disorders (10038738)	Apparent life threatening event (10065044)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Asphyxia (10003497)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Laryngospasm (10023891)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Rhinitis allergic (10039085)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
Skin and subcutaneous tissue disorders (10040785)	Dermatitis atopic (10012438)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7
	Rash (10037844)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Urticaria (10046735)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1

ACWY_3 = Subjects who received 3 primary doses of MenACWY-TT at 2, 3 and 4 months of age
ACWY_2 = Subjects who received 2 primary doses of MenACWY-TT at 2 and 4 months of age
MenCCRM = Subjects who received 2 primary doses of *Menjugate* at 2 and 4 months of age

MenC-TT = Subjects who received 2 primary doses of *NeisVac-C* at 2 and 4 months of age
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

CHMP comment: for serious adverse events, respiratory tract infection and gastroenteritis are notable though appear to occur in all 4 treatment groups. The number of instances is too small to state that these may be more common (or not) upon exposure to the current product.

Serious Adverse Events from primary vaccination up to end of Extended Safety Follow-Up

Report Final

Table 382 Percentage of subjects reporting Serious Adverse Events classified by MedDRA Primary System Organ Class and Preferred Term from primary vaccination up to end of ESFU (Primary Total Vaccinated cohort)

		ACWY_3 N = 528				ACWY_2 N = 524				MenCCRM N = 516				MenC-TT N = 527			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		54	10.2	7.8	13.1	56	10.7	8.2	13.7	45	8.7	6.4	11.5	52	9.9	7.5	12.7
Blood and lymphatic system disorders (10005329)	Lymphadenitis (10025188)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	1	0.2	0.0	1.1	0	0.0	0.0	0.7
Cardiac disorders (10007541)	Wolff-parkinson-white syndrome (10048015)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7
Congenital, familial and genetic disorders (10010331)	Laryngomalacia (10060786)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Plagiocephaly (10048586)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
Eye disorders (10015919)	Conjunctivitis allergic (10010744)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
Gastrointestinal disorders (10017947)	Aphthous stomatitis (10002958)	0	0.0	0.0	0.7	2	0.4	0.0	1.4	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Diarrhoea (10012735)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Enteritis (10014866)	0	0.0	0.0	0.7	3	0.6	0.1	1.7	1	0.2	0.0	1.1	1	0.2	0.0	1.1
	Gastrooesophageal reflux disease (10017885)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7
	Haematemesis (10018830)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Inguinal hernia (10022016)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7
	Inguinal hernia, obstructive (10022021)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Vomiting (10047700)	2	0.4	0.0	1.4	1	0.2	0.0	1.1	0	0.0	0.0	0.7	1	0.2	0.0	1.1
General disorders and administration site conditions (10018065)	Pyrexia (10037660)	0	0.0	0.0	0.7	5	1.0	0.3	2.2	0	0.0	0.0	0.7	3	0.6	0.1	1.7
Immune system disorders (10021428)	Milk allergy (10027633)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
Infections and infestations (10021881)	Abscess (10000269)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7
	Adenovirus infection (10060931)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Anal abscess (10048946)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Atypical pneumonia (10003757)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Bacteraemia (10003997)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Bacterial pyelonephritis (10059517)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7	2	0.4	0.0	1.4
	Bronchiolitis (10006448)	12	2.3	1.2	3.9	10	1.9	0.9	3.5	9	1.7	0.8	3.3	14	2.7	1.5	4.4
	Bronchitis (10006451)	9	1.7	0.8	3.2	4	0.8	0.2	1.9	1	0.2	0.0	1.1	8	1.5	0.7	3.0
	Bronchopneumonia (10006469)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	4	0.8	0.2	2.0	1	0.2	0.0	1.1
	Cellulitis (10007882)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Conjunctivitis (10010741)	1	0.2	0.0	1.1	1	0.2	0.0	1.1	1	0.2	0.0	1.1	1	0.2	0.0	1.1
	Conjunctivitis bacterial (10061784)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7

		ACWY_3 N = 528				ACWY_2 N = 524				MenCCRM N = 516				MenC-TT N = 527			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Croup infectious (10011416)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Encephalitis (10014581)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Epstein-barr virus infection (10015108)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Escherichia urinary tract infection (10052238)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Exanthema subitum (10015586)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Gastroenteritis (10017888)	6	1.1	0.4	2.5	3	0.6	0.1	1.7	5	1.0	0.3	2.2	3	0.6	0.1	1.7
	Gastroenteritis bacterial (10061166)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7
	Gastroenteritis norovirus (10068189)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Gastroenteritis rotavirus (10017913)	2	0.4	0.0	1.4	2	0.4	0.0	1.4	1	0.2	0.0	1.1	2	0.4	0.0	1.4
	Gastroenteritis salmonella (10017914)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7
	Genital candidiasis (10018143)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	H1n1 influenza (10069767)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Hand-foot-and-mouth disease (10019113)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7
	Herpes simplex (10019948)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Influenza (10022000)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Intervertebral discitis (10060738)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Laryngitis (10023874)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Lung infection (10061229)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Nasopharyngitis (10028810)	0	0.0	0.0	0.7	2	0.4	0.0	1.4	1	0.2	0.0	1.1	0	0.0	0.0	0.7
	Oral candidiasis (10030963)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Oral herpes (10067152)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Osteomyelitis (10031252)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Otitis media (10033078)	3	0.6	0.1	1.7	0	0.0	0.0	0.7	2	0.4	0.0	1.4	1	0.2	0.0	1.1
	Otitis media acute (10033079)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	2	0.4	0.0	1.4
	Pertussis (10034738)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Pharyngitis (10034835)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Pneumonia (10035664)	3	0.6	0.1	1.7	3	0.6	0.1	1.7	2	0.4	0.0	1.4	4	0.8	0.2	1.9
	Pneumonia bacterial (10060946)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Pneumonia respiratory syncytial viral (10035732)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Pyelonephritis (10037596)	1	0.2	0.0	1.1	1	0.2	0.0	1.1	1	0.2	0.0	1.1	4	0.8	0.2	1.9

		ACWY_3 N = 528				ACWY_2 N = 524				MenCCRM N = 516				MenC-TT N = 527			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Pyelonephritis acute (10037597)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Respiratory syncytial virus bronchiolitis (10038718)	2	0.4	0.0	1.4	3	0.6	0.1	1.7	2	0.4	0.0	1.4	0	0.0	0.0	0.7
	Respiratory syncytial virus infection (10061603)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Rotavirus infection (10067470)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Sepsis (10040047)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Tonsillitis (10044008)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Upper respiratory tract infection (10046306)	4	0.8	0.2	1.9	2	0.4	0.0	1.4	2	0.4	0.0	1.4	1	0.2	0.0	1.1
	Urinary tract infection (10046571)	3	0.6	0.1	1.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7	2	0.4	0.0	1.4
	Viral infection (10047461)	2	0.4	0.0	1.4	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Viral rash (10047476)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7
Injury, poisoning and procedural complications (10022117)	Concussion (10010254)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	4	0.8	0.2	2.0	2	0.4	0.0	1.4
	Contusion (10050584)	1	0.2	0.0	1.1	1	0.2	0.0	1.1	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Joint dislocation (10023204)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7
	Near drowning (10056905)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7
	Overdose (10033295)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Skull fracture (10061365)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Thermal burn (10053615)	2	0.4	0.0	1.4	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7
Investigations (10022891)	Alanine aminotransferase increased (10001551)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Aspartate aminotransferase increased (10003481)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Blood alkaline phosphatase increased (10059570)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
Metabolism and nutrition disorders (10027433)	Decreased appetite (10061428)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
Musculoskeletal and connective tissue disorders (10028395)	Arthritis (10003246)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Muscle spasms (10028334)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7
	Sacroiliitis (10039361)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7
	Torticollis (10044074)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	Cerebral haemangioma (10048788)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1

		ACWY_3 N = 528				ACWY_2 N = 524				MenCCRM N = 516				MenC-TT N = 527			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Nervous system disorders (10029205)	Brain injury (10067967)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Epilepsy (10015037)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	1	0.2	0.0	1.1	1	0.2	0.0	1.1
	Febrile convulsion (10016284)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	1	0.2	0.0	1.1	2	0.4	0.0	1.4
	Hypotonia (10021118)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7
Psychiatric disorders (10037175)	Breath holding (10006322)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
Renal and urinary disorders (10038359)	Haematuria (10018867)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7
Reproductive system and breast disorders (10038604)	Balanoposthitis (10004078)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7
	Testicular retraction (10043348)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
Respiratory, thoracic and mediastinal disorders (10038738)	Apparent life threatening event (10065044)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Asphyxia (10003497)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Asthma (10003553)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Bronchial hyperreactivity (10066091)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	1	0.2	0.0	1.1	0	0.0	0.0	0.7
	Bronchospasm (10006482)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7
	Laryngospasm (10023891)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
	Rhinitis allergic (10039085)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
Skin and subcutaneous tissue disorders (10040785)	Dermatitis atopic (10012438)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7
	Rash (10037844)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	0	0.0	0.0	0.7	0	0.0	0.0	0.7
	Urticaria (10046735)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1
Vascular disorders (10047065)	Kawasaki's disease (10023320)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1

ACWY_3 = Subjects who received 3 primary doses of MenACWY-TT at 2, 3 and 4 months of age
ACWY_2 = Subjects who received 2 primary doses of MenACWY-TT at 2 and 4 months of age
MenCCRM = Subjects who received 2 primary doses of *Menjugate* at 2 and 4 months of age
MenC-TT = Subjects who received 2 primary doses of *NeisVac-C* at 2 and 4 months of age
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

CHMP comment: for serious adverse events, the pattern described for the EFSU is similar to that observed in the primary phase i.e. respiratory tract infection and gastroenteritis. The adverse events are noted but the numbers are considered to be too few to draw conclusions.

Discontinuation due to AES

Primary phase

Five subjects withdrew due to an AE or SAE during the primary phase of the study. Two subjects withdrew due to SAEs and one subject withdrew due to an AE in the ACWY_3 group, one subject withdrew due to an SAE in the MenCCRM group and one subject withdrew due to an AE in the MenC-TT group.

The three SAEs leading to withdrawal from the study were due to:

1) Apparent life threatening illness/Epstein Barr Virus (EBV)

2) Muscle spasms

3) Respiratory Syncitial Virus (RSV) bronchiolitis

None of these symptoms were determined by the investigators to be causally related to any study vaccination.

Booster phase

No adverse events led to premature discontinuation of the study in the booster phase.

Comment comment: only 5 subjects withdrew; these withdrawals occurred during the primary phase and were adjudged to be unrelated to the current product. The small number of withdrawals is not likely to affect the overall interpretation of study outcome.

2.2.3. Discussion on clinical aspects

Data submitted by the company are noted.

At this juncture, results submitted by the company suggest that the current product has clinical efficacy in promoting development of antibodies in recipients under 12 months of age against the meningococcus, as described.

Clinical safety results submitted by the company do not appear to raise any particular concern at this juncture.

Questions are not raised within the current procedure.

The company intends to submit a full clinical study report within a forthcoming variation procedure. It is considered that any questions on the clinical study report now submitted will be more appropriately raised during the forthcoming variation procedure.

3. Rapporteur's overall conclusion and recommendation

Regulatory action is not required within the current procedure. The company intends to submit a complete study report (within 18 months) in order to undertake a variation procedure and add information to the PI texts. This is acceptable.

It is considered that any questions on the clinical study report now submitted will be more appropriately raised during the forthcoming variation procedure.

☒ **Fulfilled:**

Regulatory action is not required within the current procedure.

☐ **Not fulfilled:**

4. Additional clarification requested

None