10 November 2016
EMA/CHMP/805536/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nimenrix

Common name: meningococcal group A, C, W135 and Y conjugate vaccine

Procedure No. EMEA/H/C/002226/II/0049

Note

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

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List of abbreviations

AE adverse event

ATP according-to-protocol

CI confidence interval

CLIA chemiluminescent immunoassay

CRM197 a non-toxic mutant form of Corynebacterium diphtheriae toxin

CSR clinical study report

D diphtheria

DT diphtheria toxoid

DTaP diphtheria, tetanus, and acellular pertussis

ELISA enzyme-linked immunosorbent assay

EL.U enzyme-linked immunosorbent assay unit(s)

EMA European Medicines Agency

ESFU extended safety follow-up

EU European Union

FHA filamentous haemagglutinin

GMC geometric mean concentration

GMT geometric mean titre

GSK GlaxoSmithKline Biologicals (MAH for Nimenrix until November 2015)

HBs hepatitis B surface antigen

HBV hepatitis B virus

Hib Haemophilus influenzae type b

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

IgG immunoglobulin G

IPV inactivated polio vaccine

IU international units

M month

MAH Marketing Authorisation Holder

MedDRA Medical Dictionary for Regulatory Activities

MenA Neisseria meningitidis serogroup A

MenACWY-TT meningococcal serogroups A, C, W-135, Y tetanus toxoid conjugate vaccine (developed by GSK Biologicals)

MenC Neisseria meningitidis serogroup C

MenW-135 Neisseria meningitidis serogroup W-135

MenY Neisseria meningitidis serogroup Y

MMRV measles, mumps, rubella and varicella vaccine

NOCI new onset of chronic illness(es)

PD protein D, a 42-kD cell-surface lipoprotein which is highly conserved among encapsulated and unencapsulated strains of Haemophilus influenzae

PDCO Paediatric Committee (of the European Medicines Agency)

PI Product Information

PIP paediatric investigation plan

PRN pertactin

PRP polyribosyl ribitol phosphate

PSUR periodic safety update report

PT pertussis toxoid

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

SAE serious adverse event

SBA serum bactericidal assay

SmPC summary of product characteristics

TT tetanus toxoid

TVC total vaccinated cohort

UK United Kingdom

vs versus

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Limited submitted to the European Medicines Agency on 9 December 2015 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include a wider paediatric population starting from 6 weeks of age for Nimenrix; as a consequence, sections 4.1, 4.2, 4.5, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet and the RMP are updated in accordance.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0089/2015 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0089/2015 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH (GSK) received Scientific Advice from the CHMP on 19 September 2013. The Scientific Advice pertained to clinical aspects.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

CHMP Rapporteur: Greg Markey CHMP Co-Rapporteur: Karsten Bruins Slot

PRAC Rapporteur: Rafe Suvarna

Timetable	Actual dates
Submission date	9 December 2015
Start of procedure	30 January 2016
CHMP Rapporteur's preliminary assessment report circulated on	8 February 2016
CHMP Co-Rapporteur's preliminary assessment report circulated on	23 March 2016
PRAC Rapporteur's preliminary assessment report circulated on	1 April 2016
PRAC RMP advice and assessment overview adopted by PRAC on	14 April 2016
CHMP Joint Rapporteur's updated assessment report circulated on	20 April 2016
Request for supplementary information and extension of timetable adopted by the CHMP on	28 April 2016
MAH's responses submitted to the CHMP on	14 July 2016
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	10 August 2016
2nd request for supplementary information and extension of timetable adopted by the CHMP on	15 September 2016
MAH's responses submitted to the CHMP on	11 October 2016
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	19 October 2016
CHMP opinion	10 November 2016

2. Scientific discussion

2.1. Introduction

Nimenrix is a vaccine indicated for active immunisation of individuals from the age of 12 months and above against invasive meningococcal diseases caused by Neisseria meningitidis serogroups A, C, W-135 and Y. Anti-capsular meningococcal antibodies are known to protect against meningococcal diseases via complement mediated bactericidal activity. Nimenrix induces the production of bactericidal antibodies against capsular polysaccharides of serogroups A, C, W-135 and Y, which are measured by assays using either rabbit complement (rSBA) or human complement (hSBA). Vaccine efficacy was inferred from the demonstration of immunologic non inferiority (based mainly on comparing proportions with rSBA titres at least 8) to licensed meningococcal vaccines.

This variation includes submission of the clinical study reports (CSR) on a randomised, open label, controlled, multicentre, primary vaccination study (MenACWY-TT-083) to evaluate the safety and immunogenicity of 2 vs. 3 doses of Nimenrix in infants followed by a booster dose at the age of 12 months.

As background to this variation the initial application dossier for Nimenrix included studies to support use from 12 months of age. At that time the MAH (GSK) had only data on one vs. two doses for the age group 9 to 12 months in MenACWY-TT-055/062, in which infants aged 9 months received 2 doses (the second dose when they were ~12 months old) and those aged 12 months received a single dose.

One month after vaccination (i.e. at month 4 (M4) of study) in the single dose (ACWY-1) group, 79.5% and 94.6% had hSBA-MenA and C titres ≥1:8, respectively, compared to 50.8% for MenW and 56.1% for MenY. In the ACWY-2 group the post-dose 2 (i.e. M4) percentages with hSBA ≥1:8 were at least numerically higher at 88.4%, 100%, 99.3% and 99.3% for respective meningococcal serogroups. The M4 GMTs were lower for the ACWY-1 group vs. the ACWY-2 group. Even for MenA, with the least difference between one and two doses, the 95% CI did not overlap.

By month 12 (M12) of the study the percentages with hSBA titres ≥1:8 were 87.5%, 89.4% and 80.0% for MenC, MenW-135 and Men Y, respectively, in the ACWY-1 group. Higher percentages (91.2%, 99.1% and 92.5%, respectively) had such titres in the ACWY-2 group. In contrast, against MenA 20.6% ACWY-1 and 25.9% ACWY-2 subjects had hSBA titres ≥1:8. For MenA and MenC in the ACWY-1 group and for all meningococcal serogroups in the ACWY-2 group the hSBA GMTs decreased from M1 to M12. The ACWY-1 group showed increases in the GMTs for MenW (from 11 to 128) and Y (from 15 to 56). These hSBA data suggested a possible benefit for two doses when the first was given at 9 months.

The MAH has since completed a study (MenACWY-TT-083) that compares two doses of Nimenrix at 2 and 4 months of age with 3 doses at 2, 3 and 4 months of age in infancy, each followed by a single booster dose at 12 months of age. Two control groups are used (a MenC-CRM197 conjugate and a MenC-TT conjugate). In each group the meningococcal conjugate vaccines were co-administered with Infanrix hexa (DTaP-IPV-HBV-PRP-T) and Synflorix (10-valent pneumococcal conjugate vaccine). Based on the results, the MAH proposes a 2+1 dose regimen starting from 6 weeks of age in this variation.

Some elements of the design of study MenACWY-TT-083 were discussed as part of the request for scientific advice from CHMP. In particular, the use of non-inferiority immune responses compared to licensed MencC conjugate vaccines was agreed, along with the immunological endpoints (EMEA/CHMP/SAWP/310864/2007). Study MenACWY-TT-083 is also part of the paediatric investigation plan (PIP) and its design was discussed in detail with the Paediatric Committee (PDCO). The most appropriate control vaccines were discussed and agreed during the initial PIP procedure.

2.2. Non-clinical aspects

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

2.3. Clinical aspects

2.3.1. Introduction

The application is based on a single newly reported clinical study MenACWY-TT-083. This was an open label randomised and active controlled study in infants. It was designed to demonstrate non-inferiority of the immune response to MenC elicited by Nimenrix (MenACWY-TT) when given intramuscularly at 2, 4 and 12 months of age or at 2, 3, 4 and 12 months of age compared to two licensed MenC conjugate vaccines (one CRM197 and one TT conjugate) given intramuscularly at 2, 4 and 12 months of age. The study was conducted between July 2010 and September 2013 at 44 centres in three countries (Estonia, Germany and Spain).

GCP

The Clinical trial was performed in accordance with GCP as claimed by the MAH.

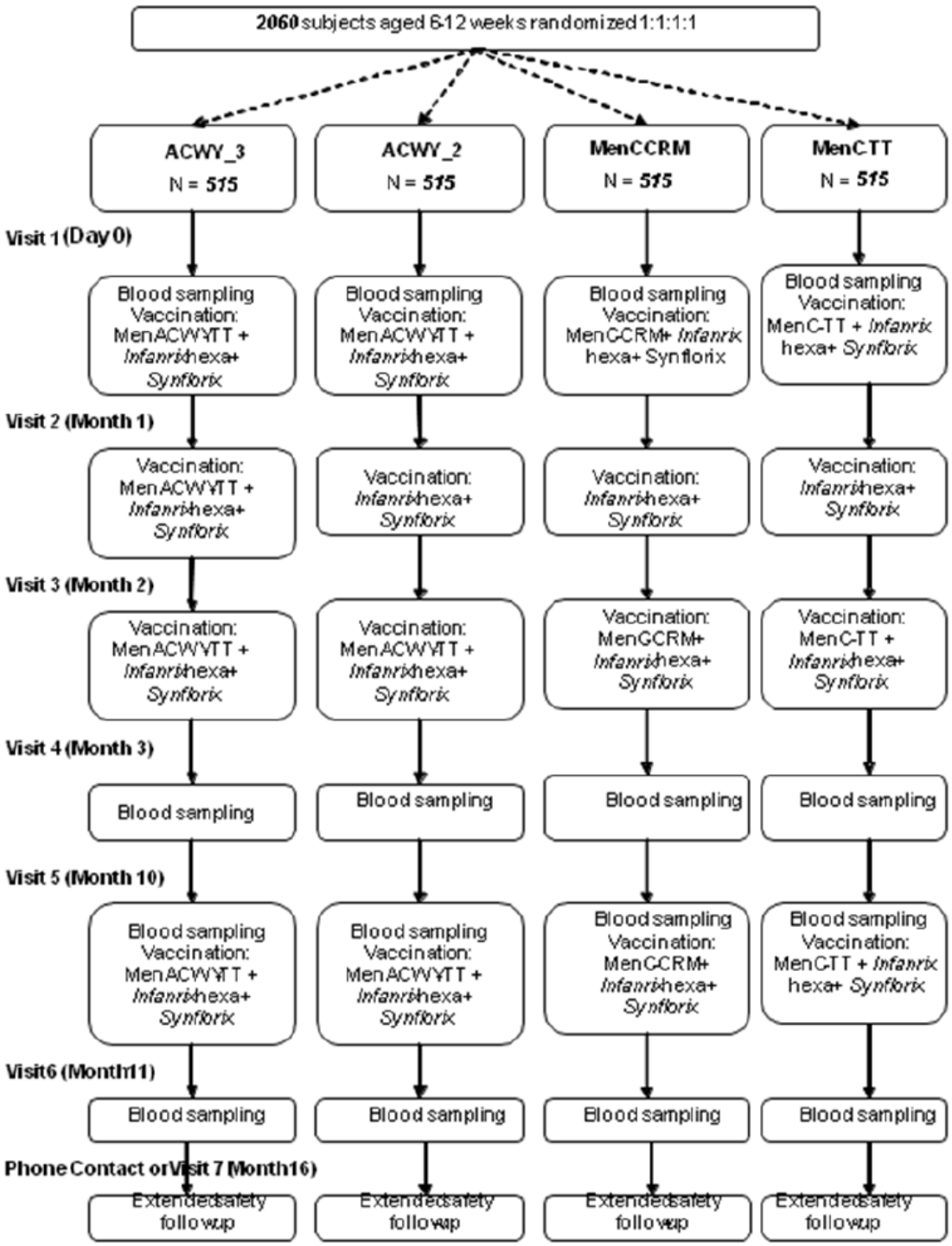
2.4. Clinical efficacy

2.4.1. Study MenACWY-TT-083

Study title: Immunogenicity and safety of GSK Biologicals' meningococcal vaccine (GSK134612) when co-administered with a pneumococcal conjugate vaccine and Infanrix hexa in healthy infants.

Methods

Table 1. Overall study plan



Study participants

The study population consisted of previously unvaccinated (except for neonatal HBV or BCG) healthy male and female infants aged between 6 and 12 weeks (42-90 days) at the time of the first vaccination and born after a gestation period of at least 36 weeks. Infants were excluded if they had received > 14 days in total of immunosuppressants or other immune-modifying drugs since birth or had any other reason to have immunodeficiency. Non-study vaccinations were not allowed except for rotavirus and influenza vaccines (at any time) and MMR[V], which was allowed due to a measles outbreak that led to relaxing the initial plan to delay administration of MMR[V] until after Visit 6. Other exclusions were standard for infant vaccination studies, including state of health at each visit that could result in deferred dosing.

Objectives

Primary objectives

The following 6 co-primary objectives were assessed in a hierarchical manner in the following order:

1. To demonstrate at 5 months of age (Visit 4) non-inferiority (5% NI margin) of the 3-dose schedule of MenACWY-TT vs. the 2-dose schedule of MenC-CRM197 (Menjugate) for percentages with rSBA-MenC ≥1:8.
2. To demonstrate at 5 months of age (Visit 4) non-inferiority (5% NI margin) of the 3-dose schedule of MenACWY-TT vs. the 2-dose schedule of MenC-TT (NeisVac-C) for percentages with rSBA-MenC≥1:8.
3. To demonstrate at 5 months of age (Visit 4) the immunogenicity of the 3-dose schedule for MenACWY-TT for MenA, W and Y based on rSBA ≥ 1:8 in at least 80%.

Objectives 4, 5 and 6 were the same as 1, 2 and 3 except that the comparisons were made for the 2-dose schedule of MenACWY-TT.

Secondary objectives

These included comparisons of rSBA at different time points, hSBA titres as measured in subsets, immune responses to the antigens in Infanrix hexa (including the anti-poliovirus titres that were submitted during the procedure) and to Synflorix. These comparisons were based on the usual cut-off values except that there was a change in the pneumococcal assay so that data are reported for 0.15 µg/ml and 0.35 µg/ml cut-offs.

Outcomes/endpoints

Primary outcome

- Immunogenicity with respect to components of the investigational vaccine:
  - rSBA titres ≥ 1:8 for each of the four serogroups in all subjects, one month after the final priming vaccination.

Secondary outcome

Immunogenicity:

- Immunogenicity with respect to components of the investigational vaccine (on secondary readouts):
  - rSBA titres ≥ 1:8 at pre-vaccination: in a randomised subset of 50% of subjects for each of the four serogroups in the investigational vaccine groups, and in a randomised subset of 50% and 25% of subjects for MenC and MenAWY, respectively, in the control groups.

- rSBA titres ≥ 1:8 at pre-booster dose and one month post-booster dose, for each of the four serogroups in all subjects.
- rSBA titres ≥ 1:128 and titres at pre-vaccination: in a randomised subset of 50% of subjects for each of the four serogroups in the investigational vaccine groups, and in a randomised subset of 50% and 25% of subjects for MenC and MenAWY, respectively, in the control groups.
- rSBA titres ≥ 1:128 and titres one month after the final priming vaccination, at pre-booster dose and one month post-booster dose, for each of the four serogroups in all subjects.
- hSBA titres ≥ 1:4, ≥ 1:8 and titres for each of the four serogroups, in a randomised subset of 50% of subjects at pre-vaccination, one month after the final priming vaccination, pre-booster dose and one month post-booster dose.

- Immunogenicity with respect to components of the co-administered pneumococcal vaccine.
  - Anti-pneumococcal antibody concentrations ≥ 0.15 µg/ml (seropositivity), ≥ 0.35 µg/ml and concentrations in a randomised subset of 25% of subjects, at pre-vaccination, one month after the final priming vaccination, pre-booster dose and one month post-booster dose.
- Immunogenicity with respect to components of the co-administered DTPa-HBV-IPV/Hib vaccine.
  - Antibody concentrations/titres for anti-diphtheria (≥0.1 IU/ml and concentrations), anti-tetanus (≥0.1 IU/ml and concentrations), anti-PT, anti- FHA, anti-PRN (≥ 5 EL.U/ml and concentrations), anti-HBs (≥10 mIU/ml, ≥100 mIU/ml and concentrations), anti-polio type 1, 2 and 3 (≥1:8 and titres), anti-PRP (≥0.15 µg/ml, ≥1.0 µg/ml and concentrations) antibodies in a randomised subset of 25% of subjects, at pre-vaccination, one month after the final priming vaccination, pre-booster and one month post-booster dose.

Sample size

The target sample size was 1650 subjects evaluable for immunogenicity (412 per vaccine group). Assuming ~20% might have withdrawn or not been evaluable for immunogenicity, the target sample size was 2060 (515 per vaccine group).

Treatment and Randomisation

The randomisation of subjects to vaccine group was performed at GSK Biologicals, Rixensart, using MATEX. Subjects were allocated using GSK's SBIR system. A randomisation block scheme was used to ensure that correct balance between treatments was maintained. The randomisation algorithm used a minimisation procedure accounting for centre. Treatments were as follows for the four groups:

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)

There was also randomisation of subjects to assay subsets as shown in the table below.

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%

Testing in each subset is explained below.

- 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 antipolio 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 antipolio 1, 2, 3 at all time points.

Laboratory assays and time-points

The assays were conducted in various laboratories as shown below. Most were conducted by GSK using previously reported methodologies that have been fully reviewed in recent years.

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

Immunological parameters used to interpret immune responses

1. Functional anti-meningococcal activity was determined by a serum bactericidal test according to the CDC protocol [Maslanka, 1997] using baby rabbit complement. Using human complement, hSBA titres of at least 1:4 broadly correlate with protection against invasive meningococcal disease due to serogroup C [Goldschneider 1969]. This same cut-off has been proposed to apply to serogroups A and B. Bactericidal antibody titres measured using baby rabbit complement are higher than those measured using human complement. Based on UK data, rSBA titres against MenC of at least 1:8 have been proposed to correlate with short-term protection [Andrews, 2003; Borrow, 2005]. However, rSBA titres of 1:128 also correlate well with hSBA titres 1:4 for MenC and a rSBA titre of 1:168 has been regarded as a more conservative correlate of protection than 1:8. Therefore, the MAH presented percentages reaching rSBA titres at least 1:8 and at least 1:128.

2. Functional anti-meningococcal activity was also determined by a serum bactericidal test using human complement (hSBA). Percentages reaching titres at least 1:4 and at least 1:8 were presented.
3. Specific antibodies against DT (anti-D) and TT (anti-TT) were measured by an ELISA developed in-house or a multiplex immuno-assay (Luminex) developed in-house. The cut-off of the tests was set at 0.1 IU/ml [Camargo, 1984; Melville-Smith, 1983]. Antibody concentrations greater than or equal to this value were considered as protective. In subjects with post-vaccination anti-D concentration <0.1 IU/ml, thepost-vaccination serum samples was to be retested using a Vero cell neutralisation test [Miyamura, 1974a; Miyamura, 1974b]. The cut-off of the Vero-cell assay was 0.016 IU/ml.
4. Antibodies against the pertussis components PT, FHA and PRN were measured by an ELISA technique developed in-house or a multiplex immuno-assay (Luminex) developed in-house. The cut-off for all three pertussis antibodies was 5 EL.U/ml. Subjects with antibody concentration below this cut-off were considered seronegative. No correlate of protection is defined for the immune response to pertussis antigens [Granstrom, 1987; Kaprinski, 1987].
5. Antibodies to HBs antigen were measured by a CLIA developed in-house. Antibody concentrations greater than or equal to 10 mIU/ml were considered protective [CDC, 1991 and WHO, 2009]. There was a change in the Hepatitis B assay at the time of testing. Antibodies to HBsAg were measured using CLIA with a cut-off of 6.2 mIU/ml.
6. Antibodies against poliovirus types 1, 2 and 3 were determined by a virus microneutralisation test adapted from the WHO Guidelines for WHO/EPI Collaborative Studies on Poliomyelitis [WHO, 1993]. The lowest dilution at which serum samples are to be tested is 1:8, from which a test is considered positive. Titres will be expressed in terms of the reverse of the dilution resulting in 50% inhibition. Antibody titres greater than or equal 1:8 are considered as protective.
7. Total antibodies against the Hib polysaccharide PRP were measured by an ELISA or multiplex developed in-house. The cut-off of the test was 0.15 µg/ml. Antibody concentrations greater than or equal to this value were considered as protective [Makela 1977].
8. Pneumococcal serotype specific total IgG antibodies (antibodies to 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) were each measured by 22F-inhibition ELISA [Concepcion, 2001]. The antibody concentration was determined by logistic log comparison of the ELISA curves with a standard reference serum 89-SF available from the US FDA for which concentration of IgG and IgM to the 10 serotypes are known in µg/ml [Quataert, 1995]. The cut-off of the assay was 0.15 µg/ml.

One extra dose of the most appropriate licensed vaccine was offered to subjects presenting with any of the following at the post-booster vaccination time point:

- anti-PRP antibody concentration < 0.15 µg/ml,
- rSBA-MenC antibody titre < 1:8,
- anti-D or anti-TT antibody concentration < 0.1 IU/ml,
- anti-PT, anti-FHA or anti-PRN antibody concentration < 5 EL.U/ml,
- anti-HBs antibody concentration < 10 mIU/ml,
- anti-poliovirus types 1, 2 or 3 antibody titres < 1:8.

As no immunological correlate of protection had been defined for pneumococcal serotypes, no extra dose of a pneumococcal vaccine was to be offered.

Blinding (masking)

This was an open study. However, the laboratory in charge of testing was blinded to treatment assignment. Codes were used to link the subject and study to each sample.

Statistical methods

The co-primary objectives (1-6 as stated above) were to be assessed in a hierarchical manner. A co-primary objective could only be met if the statistical criterion for that objective was met as well as the statistical criteria for all previous co-primary objectives. For this reason, the multiplicity of objectives did not require an alpha adjustment. However, it impacted the beta parameter as Objective 6 could only be reached if all six objectives were met simultaneously. The global power to meet all primary objectives considering a sample size of 412 evaluable subjects per group was at least 82.3%.

Analysis sets

- The Primary Total Vaccinated Cohort included all vaccinated subjects during the primary phase.
- The Primary Total Vaccinated Cohort for Immunogenicity included vaccinated subjects from the primary phase with immunogenicity data.
- The Primary ATP cohort for safety included all vaccinated subjects who met the selection criteria
- The Primary ATP cohort for immunogenicity included all evaluable subjects from the Primary ATP cohort for safety who did not receive forbidden medications, had no medical condition which might have influenced the immune response, complied with the vaccination schedule for Visits 1, 2 and 3 and the blood sample schedule for Visit 4.
- The Booster Total Vaccinated cohort included all subjects who received a booster dose at Visit 5.
- The Booster Total Vaccinated cohort for immunogenicity included all who received a booster dose with post-booster immunogenicity data.
- The Booster ATP cohorts for safety and immunogenicity were defined as for the primary cohorts with addition of having a blood sample from Visit 6. The interval between the Visit 5 and 6 blood samples was to be 21 to 48 days.

The primary analyses of immunogenicity were based on the defined ATP immunogenicity cohorts.

All CI computed were two-sided 95% CI. The exact 95% CIs for a proportion within a group were calculated based on the method by Clopper. The standardised asymptotic 95% CI for the group difference in proportions were based on the method of 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. The 95% CIs of the group GMC/GMT ratios were computed using an ANOVA model on the log10 transformation of the concentrations/titres. The ANOVA model included the vaccine group as fixed effect.

The final analysis was performed on the data collected up to one month after the booster vaccine dose (administered at Visit 5) and used cleaned data.

2.4.1.1. Results

Recruitment, Conduct of the study and numbers analysed

The first subject was enrolled on 01 July 2010 and the last study visit was on 10 September 2013.

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

- Amendment 1 (06 December 2010) included some administrative changes.
- Amendment 2 (25 May 2011) increased the sample size by approximately 50% so that 680 additional subjects were to be enrolled to reach 1650 evaluable subjects. Testing for *S. pneumoniae* OPA was removed.
- Amendment 3 (30 July 2012) allowed administration of MMR or MMRV vaccine throughout the study to address a measles outbreak in Spain.

Most (1559) of the 2095 subjects were enrolled in Spain, followed by 502 in Germany and 34 in Estonia. Of these, 2042 subjects completed the primary phase and 1841 were included in the primary ATP immunogenicity cohort. Most of the exclusions were due to missing immunogenicity data (148) or due to lack of adherence to the vaccination (41) or sampling (25) schedules. The mean age of the subjects in the primary ATP cohort for immunogenicity was 8.7 weeks (range 6 to 12 weeks; median 9 weeks) with an equal gender split.

Table 2. Numbers 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

A total of 2017 subjects received a booster vaccination of which 2006 completed the booster phase, 1995 completed the study and 1815 were included in the booster ATP cohort for immunogenicity. The mean age of the subjects in the booster ATP cohort for immunogenicity was 12.1 months (range 12 to 13 months).

Baseline data

Primary vaccination phase

Across all vaccine groups, the mean age of the subjects at the first vaccination in the primary TVC was 8.6 weeks (standard deviation [SD] ±1.5). The distribution of males and females was similar, with 50.2% male and 49.8% female. By race, the majority of subjects were of White Caucasian/European heritage (94.4%).

Booster phase

Across all vaccine groups, the mean age of the subjects at the time of booster vaccination in the booster TVC was 12.1 months (SD ±0.4). The distribution of males and females was similar, with 50.1% male and 49.9% female. By race, the majority of subjects were of White Caucasian/European heritage (94.5%).

Outcomes and estimation

Immune responses to meningococcal polysaccharides

In accordance with the pre-defined criteria, non-inferiority of the 3-dose schedule of MenACWY-TT was demonstrated vs. MenC-CRM and MenC-TT.

								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

								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

The lower confidence interval limits around the percentages with rSBA titres ≥1:8 in the ACWY_3 group were >80% for each meningococcal serogroup. This finding also applied to percentages in the 3-dose group with titres ≥1:128 except for MenY (76.6%).

Except for MenA, the GMTs were numerically lower for 3 vs. 2 doses of MenACWY-TT. GMTs for MenC were significantly lower for the 3-dose group compared to the MenC-CRM197 and MenC-TT groups as well as vs. the MenACWY-TT 2-dose group (95% CI did not overlap).

Table 3. Number and percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY antibody titre equal 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

PIII(M3): time point for blood sampling one month after the primary vaccination

Non-inferiority of the 2-dose schedule of MenACWY-TT was demonstrated vs. MenC-CRM197 and MenC-TT and the lower confidence interval limits for percentages with rSBA titres ≥ 1:8 were >80% for each meningococcal serogroup. This finding also applied to percentages in the 2-dose group with titres ≥1:128 except for MenA (78.2%). The MenC GMT was significantly lower for the 2-dose MenACWY-TT group vs. the monovalent MenC vaccines (95% CI did not overlap).

								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

								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

Further exploration of the rSBA MenC GMTs indicated that the 95% CI around the GMTs for the MenACWY-TT 2-dose and 3-dose groups vs. the monovalent MenC conjugate vaccines all fell below 0.80 and, except for 2 doses vs. MenC-CRM197, were ≤0.60.

The results by country suggested lower responses in Estonia based on percentages with ≥1:128 and GMTs but there were very few subjects so such comparisons are not robust.

The hSBA titres are summarised below and demonstrate a very similar pattern of between-group comparisons as described for the rSBA data.

Table 4. Number and percentage of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY antibody titre equal to or above 1:4 and 1:8 and GMTs (primary cohort for immunogenicity)

				≥ 1:4				≥ 1:8				GMT		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
hSBA-MenA	ACWY_3	PRE	164	34	20.7	14.8	27.7	28	17.1	11.7	23.7	2.8	2.5	3.2
		PIII(M3)	200	197	98.5	95.7	99.7	196	98.0	95.0	99.5	240.9	207.8	279.3
	ACWY_2	PRE	166	31	18.7	13.1	25.4	19	11.4	7.0	17.3	2.7	2.4	3.0
		PIII(M3)	202	195	96.5	93.0	98.6	195	96.5	93.0	98.6	157.2	131.4	188.1
	MenCCRM	PRE	161	41	25.5	18.9	32.9	27	16.8	11.4	23.5	3.0	2.7	3.4
		PIII(M3)	172	21	12.2	7.7	18.1	15	8.7	5.0	14.0	2.5	2.2	2.7
	MenC-TT	PRE	166	34	20.5	14.6	27.4	27	16.3	11.0	22.8	2.9	2.6	3.3
		PIII(M3)	205	18	8.8	5.3	13.5	14	6.8	3.8	11.2	2.3	2.2	2.5
hSBA-MenC	ACWY_3	PRE	181	43	23.8	17.8	30.6	43	23.8	17.8	30.6	3.9	3.2	4.7
		PIII(M3)	214	213	99.5	97.4	100	213	99.5	97.4	100	765.6	647.4	905.3
	ACWY_2	PRE	178	35	19.7	14.1	26.3	35	19.7	14.1	26.3	3.6	3.0	4.4
		PIII(M3)	218	215	98.6	96.0	99.7	215	98.6	96.0	99.7	1308.3	1051.7	1627.4
	MenCCRM	PRE	168	50	29.8	23.0	37.3	49	29.2	22.4	36.7	4.9	3.9	6.2
		PIII(M3)	202	202	100	98.2	100	202	100	98.2	100	3188.1	2645.8	3841.5
	MenC-TT	PRE	185	44	23.8	17.8	30.6	42	22.7	16.9	29.4	3.9	3.2	4.7
		PIII(M3)	226	226	100	98.4	100	226	100	98.4	100	2626.5	2218.9	3109.0
hSBA-MenW-135	ACWY_3	PRE	182	50	27.5	21.1	34.6	49	26.9	20.6	34.0	5.0	3.9	6.3
		PIII(M3)	201	197	98.0	95.0	99.5	197	98.0	95.0	99.5	190.9	160.0	227.8
	ACWY_2	PRE	184	46	25.0	18.9	31.9	44	23.9	17.9	30.7	4.7	3.8	6.0
		PIII(M3)	217	217	100	98.3	100	217	100	98.3	100	753.5	643.8	881.8
	MenCCRM	PRE	190	54	28.4	22.1	35.4	52	27.4	21.2	34.3	5.0	4.0	6.3
		PIII(M3)	205	6	2.9	1.1	6.3	4	2.0	0.5	4.9	2.1	2.0	2.3
	MenC-TT	PRE	187	37	19.8	14.3	26.2	36	19.3	13.9	25.6	3.7	3.1	4.6
		PIII(M3)	204	3	1.5	0.3	4.2	3	1.5	0.3	4.2	2.1	2.0	2.3
hSBA-MenY	ACWY_3	PRE	191	73	38.2	31.3	45.5	73	38.2	31.3	45.5	8.0	6.1	10.5
		PIII(M3)	209	187	89.5	84.5	93.3	185	88.5	83.4	92.5	66.5	53.7	82.2
	ACWY_2	PRE	192	73	38.0	31.1	45.3	72	37.5	30.6	44.8	8.0	6.1	10.5
		PIII(M3)	214	209	97.7	94.6	99.2	209	97.7	94.6	99.2	328.1	275.8	390.2
	MenCCRM	PRE	204	71	34.8	28.3	41.8	71	34.8	28.3	41.8	7.1	5.5	9.2
		PIII(M3)	204	11	5.4	2.7	9.4	11	5.4	2.7	9.4	2.4	2.1	2.7
	MenC-TT	PRE	192	78	40.6	33.6	47.9	77	40.1	33.1	47.4	8.1	6.3	10.4
		PIII(M3)	196	5	2.6	0.8	5.9	4	2.0	0.6	5.1	2.1	2.0	2.2

The percentages with MenC hSBA titres ≥1:4 and 1:8 were comparable between each MenACWY-TT and monovalent MenC conjugate groups with lower 95% CI around the differences all within -4%. The comparisons of GMTs showed upper 95% CI that fell below 0.7 and, except for the 2-dose group vs. MenC-TT, below 0.6.

Before and after the booster dose, the rSBA titres were generally comparable between the 2-dose and 3-dose MenACWY-TT groups. Exceptions were higher GMTs for MenW and MenY in the 2-dose vs. 3-dose group with non-overlapping 95% CI.

Comparisons with the monovalent MenC groups showed similar proportions with pre- and post-boost titres ≥1:8 and ≥1:128 across the four groups with lower 95% CI within -4%. GMTs were similar for the two MenACWY-TT and MenC-CRM197 groups but lower for all 3 vs. MenC-TT with 95% CI that did not overlap. The post-boost results were similar for Spain and Germany.

Table 5. Number and percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 or rSBA-MenY antibody titre equal or above 1:8 and 1:128 and GMTs (booster 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	214	2	0.9	0.1	3.3	1	0.5	0.0	2.6	4.1	4.0	4.2
		PIII(M3)	423	420	99.3	97.9	99.9	366	86.5	82.9	89.6	243.7	220.9	268.8
		PIII(M10)	438	300	68.5	63.9	72.8	107	24.4	20.5	28.7	22.9	19.8	26.5
		PIV(M11)	439	437	99.5	98.4	99.9	433	98.6	97.0	99.5	1417.6	1281.4	1568.3
	ACWY_2	PRE	224	3	1.3	0.3	3.9	0	0.0	0.0	1.6	4.1	4.0	4.2
		PIII(M3)	438	426	97.3	95.3	98.6	360	82.2	78.3	85.7	206.1	183.5	231.4
		PIII(M10)	455	279	61.3	56.7	65.8	99	21.8	18.1	25.8	19.5	16.8	22.6
		PIV(M11)	462	460	99.6	98.4	99.9	456	98.7	97.2	99.5	1561.0	1412.3	1725.3
	MenCCRM	PRE	103	1	1.0	0.0	5.3	0	0.0	0.0	3.5	4.1	3.9	4.2
		PIII(M3)	423	7	1.7	0.7	3.4	4	0.9	0.3	2.4	4.2	4.0	4.4
		PIII(M10)	436	26	6.0	3.9	8.6	11	2.5	1.3	4.5	4.7	4.3	5.0
		PIV(M11)	446	21	4.7	2.9	7.1	8	1.8	0.8	3.5	4.6	4.3	4.9
	MenC-TT	PRE	105	2	1.9	0.2	6.7	0	0.0	0.0	3.5	4.1	4.0	4.2
		PIII(M3)	438	3	0.7	0.1	2.0	1	0.2	0.0	1.3	4.1	4.0	4.2
		PIII(M10)	453	23	5.1	3.2	7.5	3	0.7	0.1	1.9	4.4	4.2	4.6
		PIV(M11)	458	19	4.1	2.5	6.4	12	2.6	1.4	4.5	4.7	4.3	5.0
rSBA-MenC	ACWY_3	PRE	215	11	5.1	2.6	9.0	1	0.5	0.0	2.6	4.3	4.1	4.6
		PIII(M3)	422	420	99.5	98.3	99.9	386	91.5	88.4	94.0	386.0	345.1	431.7
		PIII(M10)	441	324	73.5	69.1	77.5	108	24.5	20.5	28.8	25.7	22.3	29.6
		PIV(M11)	439	437	99.5	98.4	99.9	432	98.4	96.7	99.4	1154.6	1034.1	1289.0
	ACWY_2	PRE	225	11	4.9	2.5	8.6	1	0.4	0.0	2.5	4.3	4.1	4.5
		PIII(M3)	438	432	98.6	97.0	99.5	410	93.6	90.9	95.7	598.8	526.5	681.1
		PIII(M10)	459	348	75.8	71.6	79.7	183	39.9	35.4	44.5	43.7	37.4	51.1
		PIV(M11)	463	462	99.8	98.8	100	454	98.1	96.3	99.1	1177.0	1059.1	1308.0
	MenCCRM	PRE	205	17	8.3	4.9	12.9	7	3.4	1.4	6.9	5.1	4.5	5.7
		PIII(M3)	423	421	99.5	98.3	99.9	406	96.0	93.6	97.6	949.7	837.6	1076.7
		PIII(M10)	441	229	51.9	47.2	56.7	79	17.9	14.4	21.8	16.0	13.8	18.5
		PIV(M11)	446	439	98.4	96.8	99.4	426	95.5	93.2	97.2	1051.4	919.6	1202.1
	MenC-TT	PRE	213	14	6.6	3.6	10.8	5	2.3	0.8	5.4	4.8	4.3	5.3
		PIII(M3)	439	439	100	99.2	100	438	99.8	98.7	100	1169.2	1061.2	1288.3
		PIII(M10)	451	356	78.9	74.9	82.6	195	43.2	38.6	48.0	49.3	42.1	57.7
		PIV(M11)	459	459	100	99.2	100	457	99.6	98.4	99.9	1960.2	1776.4	2163.1
rSBA-MenW-135	ACWY_3	PRE	202	7	3.5	1.4	7.0	0	0.0	0.0	1.8	4.3	4.1	4.5
		PIII(M3)	422	416	98.6	96.9	99.5	396	93.8	91.1	95.9	1093.5	944.3	1266.3
		PIII(M10)	441	372	84.4	80.6	87.6	221	50.1	45.3	54.9	68.7	58.3	81.0
		PIV(M11)	437	433	99.1	97.7	99.8	430	98.4	96.7	99.4	1955.9	1729.6	2211.9
	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)	437	434	99.3	98.0	99.9	419	95.9	93.6	97.5	1601.6	1378.4	1860.9
		PIII(M10)	459	417	90.8	87.8	93.3	254	55.3	50.7	59.9	97.7	83.3	114.5
		PIV(M11)	462	461	99.8	98.8	100	457	98.9	97.5	99.6	2777.2	2485.1	3103.6
	MenCCRM	PRE	102	6	5.9	2.2	12.4	1	1.0	0.0	5.3	4.5	4.0	5.0
		PIII(M3)	421	9	2.1	1.0	4.0	8	1.9	0.8	3.7	4.5	4.1	4.8
		PIII(M10)	440	18	4.1	2.4	6.4	16	3.6	2.1	5.8	4.7	4.4	5.1
		PIV(M11)	445	34	7.6	5.3	10.5	31	7.0	4.8	9.7	5.5	5.0	6.1
	MenC-TT	PRE	111	3	2.7	0.6	7.7	1	0.9	0.0	4.9	4.3	3.9	4.7
		PIII(M3)	438	9	2.1	0.9	3.9	5	1.1	0.4	2.6	4.3	4.1	4.6
		PIII(M10)	453	27	6.0	4.0	8.6	22	4.9	3.1	7.3	5.0	4.6	5.5
		PIV(M11)	459	37	8.1	5.7	10.9	31	6.8	4.6	9.4	5.6	5.0	6.2

				≥ 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-MenY	ACWY_3	PRE	202	3	1.5	0.3	4.3	0	0.0	0.0	1.8	4.1	4.0	4.2
		PIII(M3)	422	393	93.1	90.3	95.3	338	80.1	76.0	83.8	269.8	227.1	320.6
		PIII(M10)	441	364	82.5	78.7	86.0	126	28.6	24.4	33.0	35.4	30.6	41.0
		PIV(M11)	439	436	99.3	98.0	99.9	419	95.4	93.1	97.2	630.6	564.1	705.1
	ACWY_2	PRE	218	5	2.3	0.7	5.3	3	1.4	0.3	4.0	4.2	4.0	4.5
		PIII(M3)	438	431	98.4	96.7	99.4	394	90.0	86.7	92.6	489.8	424.9	564.6
		PIII(M10)	459	383	83.4	79.7	86.7	168	36.6	32.2	41.2	47.0	40.3	54.7
		PIV(M11)	462	459	99.4	98.1	99.9	445	96.3	94.2	97.8	881.3	787.5	986.4
	MenCCRM	PRE	103	8	7.8	3.4	14.7	2	1.9	0.2	6.8	4.8	4.2	5.5
		PIII(M3)	423	13	3.1	1.6	5.2	10	2.4	1.1	4.3	4.4	4.2	4.7
		PIII(M10)	440	54	12.3	9.4	15.7	41	9.3	6.8	12.4	6.5	5.7	7.4
		PIV(M11)	445	45	10.1	7.5	13.3	37	8.3	5.9	11.3	6.1	5.4	6.8
	MenC-TT	PRE	111	3	2.7	0.6	7.7	1	0.9	0.0	4.9	4.2	3.9	4.6
		PIII(M3)	439	13	3.0	1.6	5.0	12	2.7	1.4	4.7	4.5	4.2	4.8
		PIII(M10)	451	47	10.4	7.8	13.6	37	8.2	5.8	11.1	6.0	5.4	6.8
		PIV(M11)	461	40	8.7	6.3	11.6	34	7.4	5.2	10.2	5.8	5.2	6.6

The pre- and post-boost hSBA data showed comparable titres between the MenACWY-TT 2-dose and 3-dose groups. The GMTs for MenW and MenY were higher in the 2-dose group but the 95% CI overlapped (only just for MenW). For MenC the GMTs were higher in the two monovalent groups but the 95% CI overlapped for all between-group comparisons.

Table 6. Number and percentage of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135 or hSBA-MenY antibody titre equal to or above 1:4 and 1:8 and GMTs (Booster ATP cohort for immunogenicity)

				≥ 1:4				≥ 1:8				GMT		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
hSBA-MenA	ACWY_3	PRE	155	36	23.2	16.8	30.7	29	18.7	12.9	25.8	2.9	2.6	3.3
		PIII(M3)	188	186	98.9	96.2	99.9	185	98.4	95.4	99.7	236.0	203.6	273.5
		PIII(M10)	193	142	73.6	66.8	79.6	141	73.1	66.2	79.2	32.0	24.2	42.2
		PIV(M11)	212	210	99.1	96.6	99.9	210	99.1	96.6	99.9	1192.7	978.4	1453.9
	ACWY_2	PRE	167	34	20.4	14.5	27.3	20	12.0	7.5	17.9	2.8	2.5	3.0
		PIII(M3)	199	193	97.0	93.6	98.9	193	97.0	93.6	98.9	164.0	136.8	196.6
		PIII(M10)	204	119	58.3	51.2	65.2	119	58.3	51.2	65.2	14.5	11.2	18.7
		PIV(M11)	214	213	99.5	97.4	100	213	99.5	97.4	100	1007.2	835.7	1213.8
	MenCCRM	PRE	159	41	25.8	19.2	33.3	25	15.7	10.4	22.3	3.0	2.7	3.4
		PIII(M3)	159	18	11.3	6.8	17.3	13	8.2	4.4	13.6	2.4	2.2	2.7
		PIII(M10)	188	28	14.9	10.1	20.8	26	13.8	9.2	19.6	2.7	2.4	3.0
		PIV(M11)	204	50	24.5	18.8	31.0	50	24.5	18.8	31.0	3.9	3.3	4.6
	MenC-TT	PRE	160	33	20.6	14.6	27.7	26	16.3	10.9	22.9	2.9	2.6	3.2
		PIII(M3)	190	17	8.9	5.3	13.9	13	6.8	3.7	11.4	2.3	2.2	2.5
		PIII(M10)	202	26	12.9	8.6	18.3	26	12.9	8.6	18.3	2.7	2.4	3.1
		PIV(M11)	205	55	26.8	20.9	33.4	55	26.8	20.9	33.4	4.2	3.5	5.0
hSBA-MenC	ACWY_3	PRE	172	42	24.4	18.2	31.5	42	24.4	18.2	31.5	3.7	3.1	4.4
		PIII(M3)	199	198	99.5	97.2	100	198	99.5	97.2	100	720.6	602.4	862.1
		PIII(M10)	193	184	95.3	91.3	97.8	184	95.3	91.3	97.8	116.1	94.2	143.0
		PIV(M11)	213	212	99.5	97.4	100	212	99.5	97.4	100	4411.2	3654.5	5324.6
	ACWY_2	PRE	180	40	22.2	16.4	29.0	40	22.2	16.4	29.0	3.9	3.2	4.7
		PIII(M3)	214	211	98.6	96.0	99.7	211	98.6	96.0	99.7	1340.7	1073.1	1675.2
		PIII(M10)	208	198	95.2	91.3	97.7	198	95.2	91.3	97.7	181.4	147.3	223.4
		PIV(M11)	221	220	99.5	97.5	100	220	99.5	97.5	100	4992.3	4085.7	6100.0
	MenCCRM	PRE	169	54	32.0	25.0	39.6	53	31.4	24.5	38.9	5.2	4.1	6.6
		PIII(M3)	190	190	100	98.1	100	190	100	98.1	100	3301.2	2728.6	3994.0
		PIII(M10)	185	160	86.5	80.7	91.1	160	86.5	80.7	91.1	76.8	58.5	100.8
		PIV(M11)	216	216	100	98.3	100	216	100	98.3	100	5438.2	4412.4	6702.3
	MenC-TT	PRE	179	44	24.6	18.5	31.6	42	23.5	17.5	30.4	4.1	3.3	5.0
		PIII(M3)	211	211	100	98.3	100	211	100	98.3	100	2594.4	2176.0	3093.1
		PIII(M10)	203	196	96.6	93.0	98.6	196	96.6	93.0	98.6	213.7	174.6	261.7
		PIV(M11)	219	219	100	98.3	100	219	100	98.3	100	5542.3	4765.2	6446.2
hSBA-MenW-135	ACWY_3	PRE	170	44	25.9	19.5	33.1	43	25.3	19.0	32.5	4.7	3.7	6.0
		PIII(M3)	180	176	97.8	94.4	99.4	176	97.8	94.4	99.4	177.7	146.7	215.2
		PIII(M10)	198	196	99.0	96.4	99.9	196	99.0	96.4	99.9	248.1	210.4	292.6
		PIV(M11)	207	207	100	98.2	100	207	100	98.2	100	3944.9	3419.1	4551.7
	ACWY_2	PRE	183	51	27.9	21.5	35.0	49	26.8	20.5	33.8	5.2	4.1	6.6
		PIII(M3)	205	205	100	98.2	100	205	100	98.2	100	756.8	641.4	893.1
		PIII(M10)	203	201	99.0	96.5	99.9	201	99.0	96.5	99.9	332.4	287.3	384.5
		PIV(M11)	218	218	100	98.3	100	218	100	98.3	100	5122.7	4504.2	5826.1
	MenCCRM	PRE	181	55	30.4	23.8	37.6	52	28.7	22.3	35.9	5.5	4.3	7.0
		PIII(M3)	188	6	3.2	1.2	6.8	5	2.7	0.9	6.1	2.2	2.0	2.4
		PIII(M10)	201	1	0.5	0.0	2.7	1	0.5	0.0	2.7	2.0	2.0	2.1
		PIV(M11)	204	3	1.5	0.3	4.2	3	1.5	0.3	4.2	2.1	2.0	2.2
	MenC-TT	PRE	191	38	19.9	14.5	26.3	37	19.4	14.0	25.7	3.8	3.1	4.6
		PIII(M3)	203	3	1.5	0.3	4.3	3	1.5	0.3	4.3	2.1	2.0	2.3
		PIII(M10)	210	6	2.9	1.1	6.1	6	2.9	1.1	6.1	2.3	2.0	2.6
		PIV(M11)	206	6	2.9	1.1	6.2	6	2.9	1.1	6.2	2.3	2.1	2.7

				≥ 1:4				≥ 1:8				GMT		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
hSBA-MenY	ACWY_3	PRE	178	62	34.8	27.9	42.3	62	34.8	27.9	42.3	7.2	5.5	9.4
		PIII(M3)	189	168	88.9	83.5	93.0	167	88.4	82.9	92.6	62.8	50.3	78.4
		PIII(M10)	203	185	91.1	86.3	94.7	185	91.1	86.3	94.7	99.8	80.7	123.5
		PIV(M11)	206	206	100	98.2	100	206	100	98.2	100	2491.5	2125.8	2920.1
	ACWY_2	PRE	191	76	39.8	32.8	47.1	75	39.3	32.3	46.6	8.6	6.5	11.4
		PIII(M3)	201	196	97.5	94.3	99.2	196	97.5	94.3	99.2	327.4	273.0	392.7
		PIII(M10)	216	204	94.4	90.5	97.1	204	94.4	90.5	97.1	140.2	116.2	169.2
		PIV(M11)	217	217	100	98.3	100	217	100	98.3	100	2954.0	2497.9	3493.3
	MenCCRM	PRE	195	70	35.9	29.2	43.1	70	35.9	29.2	43.1	7.5	5.8	9.8
		PIII(M3)	184	9	4.9	2.3	9.1	9	4.9	2.3	9.1	2.4	2.1	2.6
		PIII(M10)	219	6	2.7	1.0	5.9	6	2.7	1.0	5.9	2.2	2.0	2.4
		PIV(M11)	213	7	3.3	1.3	6.7	7	3.3	1.3	6.7	2.3	2.1	2.6
	MenC-TT	PRE	197	78	39.6	32.7	46.8	78	39.6	32.7	46.8	8.0	6.2	10.4
		PIII(M3)	193	4	2.1	0.6	5.2	3	1.6	0.3	4.5	2.1	2.0	2.2
		PIII(M10)	213	10	4.7	2.3	8.5	10	4.7	2.3	8.5	2.4	2.1	2.7
		PIV(M11)	217	12	5.5	2.9	9.5	12	5.5	2.9	9.5	2.4	2.2	2.7

The comparisons of percentages with hSBA titres ≥1:4 and ≥1:8 gave lower 95% CI within 3%.

Immune responses to co-administered antigens

Anti-D and anti-TT antibody concentrations

After the primary series:

- All subjects had anti-D and anti-TT ≥0.1 IU/ml.
- The percentage with anti-D ≥1.0 IU/ml and the anti-D GMT were highest in the MenC-CRM197 group but at least 84% per group reached this titre.
- The percentage with anti-TT ≥1.0 IU/ml and the anti-T GMT were highest in the MenC-TT group but at least 95% reached this titre.

Table 7. Number and percentage of subjects with anti-D and anti-TT antibody concentrations equal to or above 0.1 IU per ml and 1.0 IU per ml and GMCs (Primary ATP cohort for immunogenicity)

				≥ 0.1 IU/ml				≥ 1.0 IU/ml				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-D	ACWY_3	PRE	116	37	31.9	23.6	41.2	4	3.4	0.9	8.6	0.092	0.077	0.110
		PIII(M3)	117	117	100	96.9	100	99	84.6	76.8	90.6	2.171	1.893	2.490
	ACWY_2	PRE	106	43	40.6	31.1	50.5	3	2.8	0.6	8.0	0.098	0.082	0.117
		PIII(M3)	113	113	100	96.8	100	100	88.5	81.1	93.7	2.640	2.274	3.065
	MenCCRM	PRE	117	56	47.9	38.5	57.3	7	6.0	2.4	11.9	0.133	0.108	0.165
		PIII(M3)	123	123	100	97.0	100	116	94.3	88.6	97.7	3.005	2.657	3.400
	MenC-TT	PRE	110	39	35.5	26.6	45.1	3	2.7	0.6	7.8	0.093	0.078	0.112
		PIII(M3)	115	115	100	96.8	100	103	89.6	82.5	94.5	2.488	2.169	2.855
anti-TT	ACWY_3	PRE	116	104	89.7	82.6	94.5	31	26.7	18.9	35.7	0.484	0.393	0.596
		PIII(M3)	117	117	100	96.9	100	114	97.4	92.7	99.5	3.137	2.790	3.527
	ACWY_2	PRE	107	91	85.0	76.9	91.2	31	29.0	20.6	38.5	0.496	0.388	0.636
		PIII(M3)	113	113	100	96.8	100	108	95.6	90.0	98.5	3.370	2.980	3.811
	MenCCRM	PRE	116	107	92.2	85.8	96.4	47	40.5	31.5	50.0	0.727	0.581	0.909
		PIII(M3)	123	123	100	97.0	100	120	97.6	93.0	99.5	2.847	2.523	3.212
	MenC-TT	PRE	111	91	82.0	73.6	88.6	34	30.6	22.2	40.1	0.500	0.387	0.647
		PIII(M3)	114	114	100	96.8	100	113	99.1	95.2	100	4.339	3.833	4.912

Pre-booster:

- At least 86% retained anti-D ≥0.1 IU/ml (97.5% in the MenC-CRM197 group) but the percentages with ≥1.0 IU/ml were from 6.1% (ACWY_3) to 21.0% (MenC-CRM197).

- At least 99% per group had anti-TT ≥0.1 IU/ml while 30.3% (MenC-CRM197 group) to 47.0% (MenC-TT group) had ≥1.0 IU/ml.

Post-booster:

- All subjects had anti-D and anti-TT ≥0.1 IU/ml.
- Percentages with anti-D ≥1.0 IU/ml ranged from 94.6% (ACWY_2) to 100% (MenC-CRM197) and the highest GMC was in the MenC-CRM197 group.
- Percentages with anti-TT ≥1.0 IU/ml were at least 99% per group and the highest GMT was observed for the MenC-TT group.

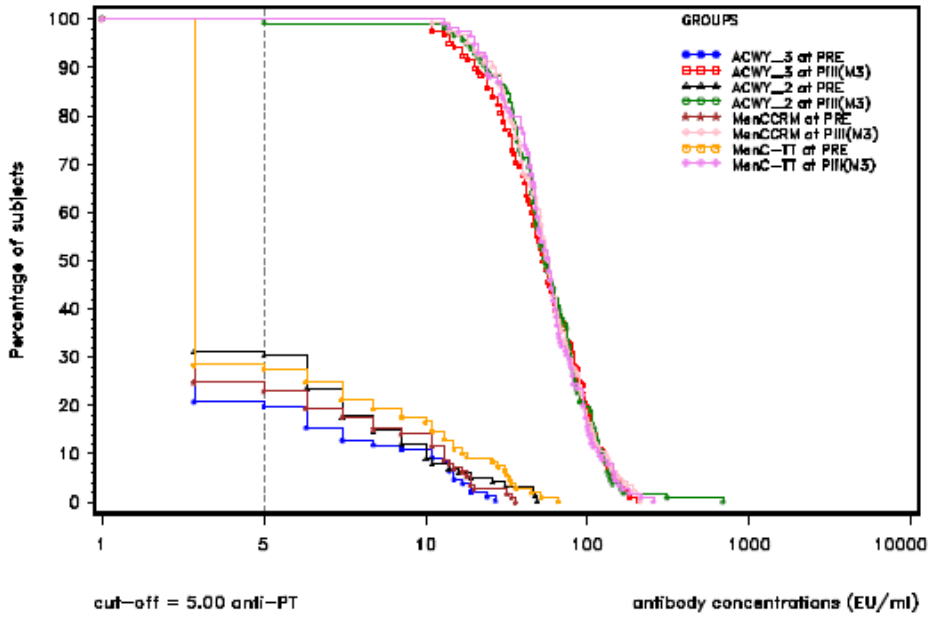
Table 8. Number and percentage of subjects with anti-D and anti-TT antibody concentrations equal to or above 0.1 IU per ml and 1.0 IU per ml and GMCs (Booster ATP cohort for immunogenicity)

				≥ 0.1 IU/ml				≥ 1.0 IU/ml				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-D	ACWY_3	PRE	110	35	31.8	23.3	41.4	5	4.5	1.5	10.3	0.093	0.077	0.112
		PIII(M3)	110	110	100	96.7	100	92	83.6	75.4	90.0	2.148	1.864	2.475
		PIII(M10)	114	98	86.0	78.2	91.8	7	6.1	2.5	12.2	0.292	0.246	0.348
		PIV(M11)	116	116	100	96.9	100	113	97.4	92.6	99.5	5.032	4.337	5.838
	ACWY_2	PRE	103	44	42.7	33.0	52.8	5	4.9	1.6	11.0	0.106	0.087	0.129
		PIII(M3)	106	106	100	96.6	100	94	88.7	81.1	94.0	2.537	2.177	2.957
		PIII(M10)	112	98	87.5	79.9	93.0	12	10.7	5.7	18.0	0.325	0.272	0.389
		PIV(M11)	111	111	100	96.7	100	105	94.6	88.6	98.0	5.438	4.600	6.430
	MenCCRM	PRE	113	55	48.7	39.2	58.3	8	7.1	3.1	13.5	0.136	0.109	0.169
		PIII(M3)	117	117	100	96.9	100	108	92.3	85.9	96.4	2.987	2.628	3.396
		PIII(M10)	119	116	97.5	92.8	99.5	25	21.0	14.1	29.4	0.507	0.433	0.594
		PIV(M11)	118	118	100	96.9	100	118	100	96.9	100	9.078	7.959	10.354
	MenC-TT	PRE	112	36	32.1	23.6	41.6	2	1.8	0.2	6.3	0.086	0.073	0.102
		PIII(M3)	113	113	100	96.8	100	103	91.2	84.3	95.7	2.570	2.245	2.942
		PIII(M10)	117	113	96.6	91.5	99.1	14	12.0	6.7	19.3	0.379	0.327	0.440
		PIV(M11)	118	118	100	96.9	100	116	98.3	94.0	99.8	6.437	5.589	7.413
anti-TT	ACWY_3	PRE	110	97	88.2	80.6	93.6	31	28.2	20.0	37.6	0.484	0.387	0.605
		PIII(M3)	110	110	100	96.7	100	107	97.3	92.2	99.4	3.125	2.772	3.523
		PIII(M10)	114	114	100	96.8	100	45	39.5	30.4	49.1	0.832	0.739	0.937
		PIV(M11)	116	116	100	96.9	100	116	100	96.9	100	10.234	9.128	11.475
	ACWY_2	PRE	104	91	87.5	79.6	93.2	34	32.7	23.8	42.6	0.571	0.444	0.733
		PIII(M3)	106	106	100	96.6	100	101	95.3	89.3	98.5	3.285	2.897	3.724
		PIII(M10)	112	111	99.1	95.1	100	45	40.2	31.0	49.9	0.780	0.677	0.898
		PIV(M11)	111	111	100	96.7	100	111	100	96.7	100	11.004	9.721	12.456
	MenCCRM	PRE	112	103	92.0	85.3	96.3	46	41.1	31.9	50.8	0.749	0.597	0.941
		PIII(M3)	117	117	100	96.9	100	113	96.6	91.5	99.1	2.832	2.501	3.206
		PIII(M10)	119	118	99.2	95.4	100	36	30.3	22.2	39.3	0.684	0.590	0.793
		PIV(M11)	118	118	100	96.9	100	117	99.2	95.4	100	8.400	7.285	9.685
	MenC-TT	PRE	113	94	83.2	75.0	89.6	36	31.9	23.4	41.3	0.516	0.401	0.664
		PIII(M3)	112	112	100	96.8	100	111	99.1	95.1	100	4.375	3.858	4.961
		PIII(M10)	117	117	100	96.9	100	55	47.0	37.7	56.5	0.956	0.835	1.094
		PIV(M11)	118	118	100	96.9	100	118	100	96.9	100	13.016	11.640	14.554

Responses to pertussis antigens

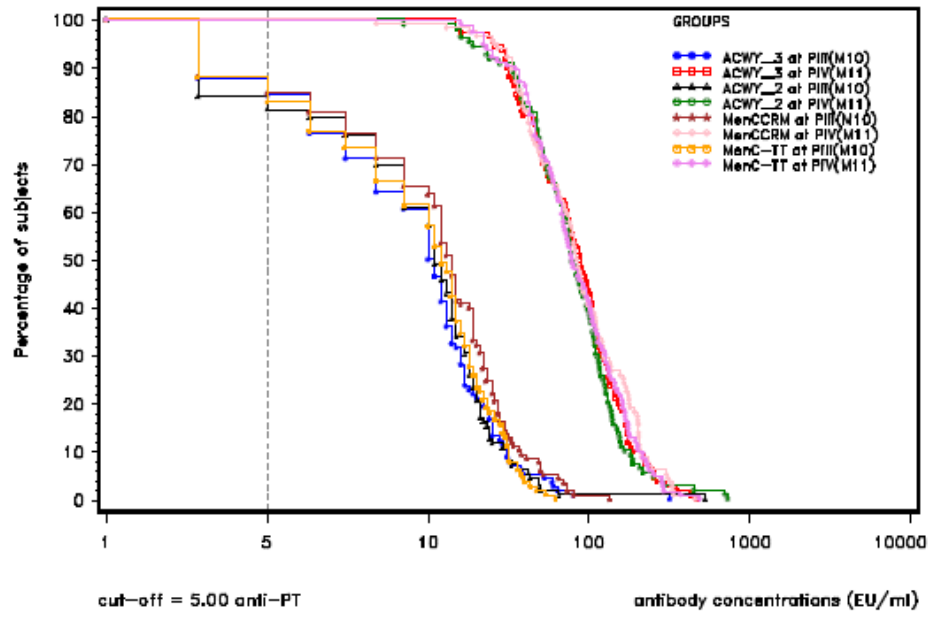
In the absence of any established ICP, the analysis was based on percentages with anti-PT, anti-FHA and anti-PRN antibody concentrations ≥ 5 EL.U/ml, the percentages classified as responders and the GMCs. These were broadly comparable between the four vaccine groups at each time point and are summarised by the figures below.

Reverse cumulative distribution curve for anti-PT antibody concentrations at pre- and post-primary vaccinations (Primary ATP cohort for immunogenicity)



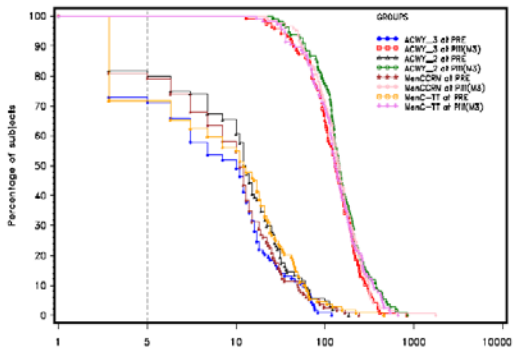
ACWY_3 = Subjects who received 3 primary doses of MenACWY-TT at 2, 3 and 4 months of age
ACWY_2 = Subjects who received 2 primary doses of MenACWY-TT at 2 and 4 months of age
MenCCRM = Subjects who received 2 primary doses of *Menjugate* at 2 and 4 months of age
MenC-TT = Subjects who received 2 primary doses of *NeisVac-C* at 2 and 4 months of age
PRE = Pre-primary vaccination at Month 0
PIII(M3) = Post primary vaccination at Month 3

Reverse cumulative distribution curve for anti-PT antibody concentrations at pre- and post-booster vaccinations (Booster ATP cohort for immunogenicity)

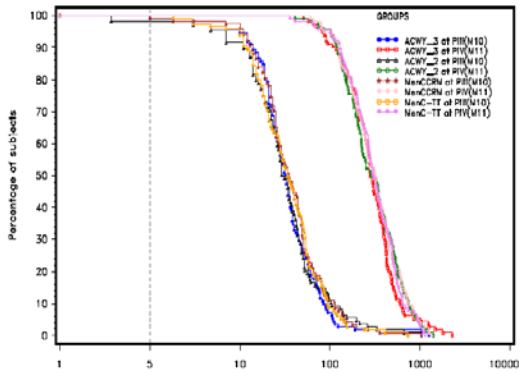


ACWY_3 = Subjects who received 3 primary doses of MenACWY-TT at 2, 3 and 4 months of age and 1 booster dose of MenACWY-TT at 12 months of age
ACWY_2 = Subjects who received 2 primary doses of MenACWY-TT at 2 and 4 months of age and 1 booster dose of MenACWY-TT at 12 months of age
MenCCRM = Subjects who 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
PIII(M10) = Pre-booster vaccination at Month 10
PIV(M11) = Post booster vaccination at Month 11

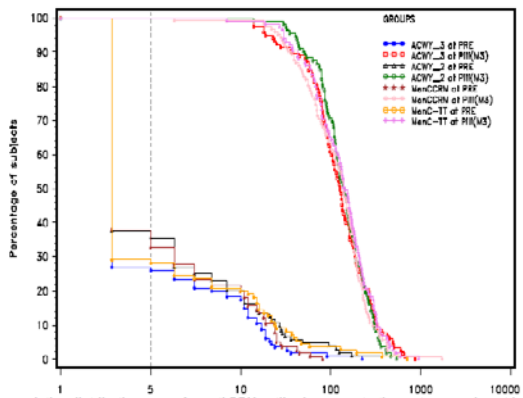
Reverse cumulative distribution curve for anti-FHA antibody concentrations at pre- and post-primary vaccinations (Primary ATP cohort for immunogenicity)



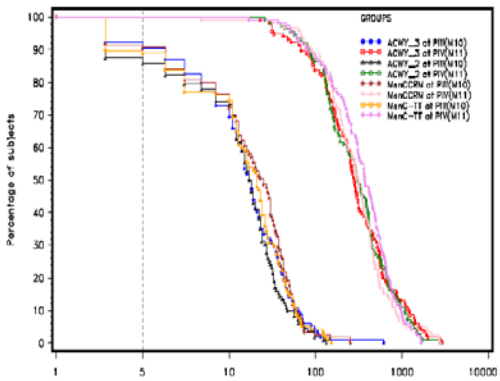
Reverse cumulative distribution curve for anti-FHA antibody concentrations at pre- and post-booster vaccinations (Booster ATP cohort for immunogenicity)



Reverse cumulative distribution curve for anti-PRN antibody concentrations at pre- and post-primary vaccinations (Primary ATP cohort for immunogenicity)



Reverse cumulative distribution curve for anti-PRN antibody concentrations at pre- and post-booster vaccinations (Booster ATP cohort for immunogenicity)



Responses to Hepatitis B antigens

There were no important differences between the four treatment groups for the post-primary, pre-boost or post-boost anti-HBsAg antibody concentrations.

Table 9. Number and percentage of subjects with anti-HBs antibody concentration equal to or above 6.2 mIU per ml, 10 mIU per ml and 100 mIU per ml and GMCs (Primary ATP cohort for immunogenicity)

				≥6.2 mIU/ml				≥10.0 mIU/ml				≥100.0 mIU/ml				GMC		
						95% CI				95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-HBs	ACWY_3	PRE	98	34	34.7	25.4	45.0	33	33.7	24.4	43.9	17	17.3	10.4	26.3	12.0	7.6	18.7
		PIII(M3)	86	85	98.8	93.7	100	85	98.8	93.7	100	74	86.0	76.9	92.6	692.3	513.2	934.0
	ACWY_2	PRE	82	36	43.9	33.0	55.3	34	41.5	30.7	52.9	14	17.1	9.7	27.0	13.7	8.4	22.4
		PIII(M3)	84	84	100	95.7	100	84	100	95.7	100	79	94.0	86.7	98.0	732.2	555.1	965.8
	MenCCRM	PRE	97	40	41.2	31.3	51.7	39	40.2	30.4	50.7	14	14.4	8.1	23.0	11.3	7.7	16.7
		PIII(M3)	94	94	100	96.2	100	94	100	96.2	100	89	94.7	88.0	98.3	848.3	663.7	1084.1
	MenC-TT	PRE	93	31	33.3	23.9	43.9	28	30.1	21.0	40.5	8	8.6	3.8	16.2	7.5	5.4	10.5
		PIII(M3)	80	79	98.8	93.2	100	79	98.8	93.2	100	73	91.3	82.8	96.4	729.5	530.3	1003.5

Table 10. Number and percentage of subjects with anti-HBs antibody concentration equal to or above 6.2 mIU/ml, 10 mIU per ml and 100 mIU per ml and GMCs (Booster ATP cohort for immunogenicity)

				≥6.2 mIU/ml				≥10.0 mIU/ml				≥100.0 mIU/ml				GMC		
						95% CI				95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-HBs	ACWY_3	PRE	91	29	31.9	22.5	42.5	28	30.8	21.5	41.3	14	15.4	8.7	24.5	10.7	6.8	17.0
		PIII(M3)	79	78	98.7	93.1	100	78	98.7	93.1	100	70	88.6	79.5	94.7	748.7	553.3	1013.1
		PIII(M10)	98	93	94.9	88.5	98.3	91	92.9	85.8	97.1	67	68.4	58.2	77.4	150.5	111.4	203.3
		PIV(M11)	97	96	99.0	94.4	100	95	97.9	92.7	99.7	93	95.9	89.8	98.9	3624.9	2570.0	5112.8
	ACWY_2	PRE	79	36	45.6	34.3	57.2	34	43.0	31.9	54.7	12	15.2	8.1	25.0	12.7	8.4	19.1
		PIII(M3)	80	80	100	95.5	100	80	100	95.5	100	75	93.8	86.0	97.9	792.6	593.3	1058.9
		PIII(M10)	91	87	95.6	89.1	98.8	86	94.5	87.6	98.2	58	63.7	53.0	73.6	138.2	99.3	192.3
		PIV(M11)	97	97	100	96.3	100	97	100	96.3	100	97	100	96.3	100	4129.8	3095.4	5509.8
	MenCCRM	PRE	93	38	40.9	30.8	51.5	37	39.8	29.8	50.5	14	15.1	8.5	24.0	11.7	7.8	17.5
		PIII(M3)	88	88	100	95.9	100	88	100	95.9	100	83	94.3	87.2	98.1	883.8	684.6	1140.8
		PIII(M10)	101	98	97.0	91.6	99.4	96	95.0	88.8	98.4	75	74.3	64.6	82.4	196.6	141.6	273.1
		PIV(M11)	103	103	100	96.5	100	103	100	96.5	100	102	99.0	94.7	100	4866.4	3723.5	6360.1
	MenC-TT	PRE	95	34	35.8	26.2	46.3	31	32.6	23.4	43.0	9	9.5	4.4	17.2	7.8	5.7	10.8
		PIII(M3)	82	81	98.8	93.4	100	81	98.8	93.4	100	75	91.5	83.2	96.5	733.9	537.6	1001.9
		PIII(M10)	100	98	98.0	93.0	99.8	94	94.0	87.4	97.8	65	65.0	54.8	74.3	141.9	106.5	189.0
		PIV(M11)	100	100	100	96.4	100	100	100	96.4	100	97	97.0	91.5	99.4	3878.7	2861.7	5257.3

Responses to Hib antigens

Differences in the anti-PRP responses emerged for percentages with anti-PRP antibody concentrations ≥ 1.0 μg/ml and the GMCs, such that the lowest response was seen in the MenC-CRM197 group after the primary doses.

Table 11. Number and percentage of subjects with anti-PRP antibody concentrations equal to or above 0.15 microgram per ml and 1.0 microgram per ml and GMCs (Primary ATP cohort for immunogenicity)

				≥ 0.15 µg/ml				≥ 1.0 µg/ml				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-PRP	ACWY_3	PRE	113	46	40.7	31.6	50.4	9	8.0	3.7	14.6	0.158	0.131	0.191
		PIII(M3)	119	119	100	96.9	100	106	89.1	82.0	94.1	4.011	3.275	4.912
	ACWY_2	PRE	106	55	51.9	42.0	61.7	19	17.9	11.2	26.6	0.213	0.168	0.270
		PIII(M3)	113	113	100	96.8	100	101	89.4	82.2	94.4	3.573	2.946	4.334
	MenCCRM	PRE	113	46	40.7	31.6	50.4	10	8.8	4.3	15.7	0.162	0.132	0.198
		PIII(M3)	123	121	98.4	94.2	99.8	94	76.4	67.9	83.6	2.752	2.144	3.534
	MenC-TT	PRE	109	47	43.1	33.7	53.0	7	6.4	2.6	12.8	0.162	0.133	0.196
		PIII(M3)	114	113	99.1	95.2	100	106	93.0	86.6	96.9	4.662	3.788	5.739

However, this pattern disappeared after the booster dose when GMCs were numerically lower for the MenACWY-TT groups but almost all subjects achieved ≥1.0 µg/ml anti-PRP.

Table 12. Number and percentage of subjects with anti-PRP antibody concentrations equal to or above 0.15 microgram per ml and 1.0 microgram per ml and GMCs (Booster ATP cohort for immunogenicity)

				≥ 0.15 µg/ml				≥ 1.0 µg/ml				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-PRP	ACWY_3	PRE	107	42	39.3	30.0	49.2	7	6.5	2.7	13.0	0.154	0.127	0.186
		PIII(M3)	111	111	100	96.7	100	98	88.3	80.8	93.6	3.775	3.059	4.658
		PIII(M10)	114	92	80.7	72.3	87.5	23	20.2	13.2	28.7	0.378	0.308	0.464
		PIV(M11)	116	116	100	96.9	100	113	97.4	92.6	99.5	17.350	14.124	21.313
	ACWY_2	PRE	103	54	52.4	42.4	62.4	16	15.5	9.1	24.0	0.207	0.164	0.261
		PIII(M3)	106	106	100	96.6	100	95	89.6	82.2	94.7	3.450	2.848	4.179
		PIII(M10)	112	91	81.3	72.8	88.0	20	17.9	11.3	26.2	0.400	0.324	0.494
		PIV(M11)	112	112	100	96.8	100	112	100	96.8	100	17.519	14.041	21.859
	MenCCRM	PRE	109	48	44.0	34.5	53.9	10	9.2	4.5	16.2	0.172	0.139	0.213
		PIII(M3)	117	115	98.3	94.0	99.8	89	76.1	67.3	83.5	2.795	2.159	3.618
		PIII(M10)	119	91	76.5	67.8	83.8	40	33.6	25.2	42.8	0.535	0.404	0.707
		PIV(M11)	119	119	100	96.9	100	119	100	96.9	100	22.879	18.147	28.847
	MenC-TT	PRE	111	50	45.0	35.6	54.8	8	7.2	3.2	13.7	0.164	0.136	0.198
		PIII(M3)	112	111	99.1	95.1	100	105	93.8	87.5	97.5	4.900	3.973	6.043
		PIII(M10)	117	100	85.5	77.8	91.3	31	26.5	18.8	35.5	0.535	0.427	0.671
		PIV(M11)	118	118	100	96.9	100	114	96.6	91.5	99.1	23.973	19.194	29.941

Responses to IPV antigens

It should be noted that all subjects received both IPV and a meningococcal conjugate vaccine. Therefore the only comparisons that can be made are with respect to any differences for the Nimenrix groups and the monovalent groups with respect to immune responses to the IPV contained in Infanrix hexa.

Bearing in mind this limitation, the relevant tables comparing 2-dose and 3-dose Nimenrix groups with the monovalent MenC groups are shown below for the post-primary time point. These tables demonstrate no disadvantages for the Nimenrix groups in terms of percentages reaching titres 1:8 to any of the 3 polioviruses. After the booster dose all subjects in all vaccine groups who were tested had titres of at least 1:8 for each poliovirus (data not shown).

Table 2 **Difference between groups (ACWY_3 and MenCCRM) in percentage of subjects with anti-Polio 1, anti-Polio 2 or anti-Polio 3 titre equal to or above 1:8, 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
anti-Polio 1	1:8	91	91	100	90	89	98.9	1.11	-2.98	6.05
anti-Polio 2	1:8	81	81	100	81	81	100	0.00	-4.55	4.55
anti-Polio 3	1:8	93	93	100	87	87	100	0.00	-3.99	4.25

Table 3 **Difference between groups (ACWY_3 and MenC-TT) in percentage of subjects with anti-Polio 1, anti-Polio 2 or anti-Polio 3 titre equal to or above 1:8, 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
anti-Polio 1	1:8	91	91	100	86	84	97.7	2.33	-1.80	8.11
anti-Polio 2	1:8	81	81	100	72	70	97.2	2.78	-1.85	9.61
anti-Polio 3	1:8	93	93	100	78	77	98.7	1.28	-2.74	6.94

Table 4 **Difference between groups (ACWY_2 and MenCCRM) in percentage of subjects with anti-Polio 1, anti-Polio 2 or anti-Polio 3 titre equal to or above 1:8, 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
anti-Polio 1	1:8	83	83	100	90	89	98.9	1.11	-3.36	6.05
anti-Polio 2	1:8	71	70	98.6	81	81	100	-1.41	-7.59	3.18
anti-Polio 3	1:8	79	79	100	87	87	100	0.00	-4.66	4.25

Table 5 **Difference between groups (ACWY_2 and MenC-TT) in percentage of subjects with anti-Polio 1, anti-Polio 2 or anti-Polio 3 titre equal to or above 1:8, 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
anti-Polio 1	1:8	83	83	100	86	84	97.7	2.33	-2.17	8.11
anti-Polio 2	1:8	71	70	98.6	72	70	97.2	1.37	-5.09	8.37
anti-Polio 3	1:8	79	79	100	78	77	98.7	1.28	-3.41	6.94

The comparisons of GMTs at the post-primary time point also generally showed no major differences. There are instances in which values are slightly higher or lower with Nimenrix.

Table 6 **Ratios of GMTs between groups (ACWY_3 and MenCCRM) for anti-Polio 1, anti-Polio 2 and anti-Polio 3, at one month post-primary vaccinations (Primary ATP cohort for immunogenicity)**

					GMT ratio (ACWY_3 / MenCCRM)		
	ACWY_3		MenCCRM			95% CI	
Antibody	N	GMT	N	GMT	Value	LL	UL
anti-Polio 1	91	279.6	90	424.1	0.66	0.46	0.94
anti-Polio 2	81	225.2	81	274.5	0.82	0.55	1.22
anti-Polio 3	93	642.7	87	674.0	0.95	0.65	1.40

Table 7 **Ratios of GMTs between groups (ACWY_3 and MenC-TT) for anti-Polio 1, anti-Polio 2 and anti-Polio 3, at one month post-primary vaccinations (Primary ATP cohort for immunogenicity)**

					GMT ratio (ACWY_3 / MenC-TT)		
	ACWY_3		MenC-TT			95% CI	
Antibody	N	GMT	N	GMT	Value	LL	UL
anti-Polio 1	91	279.6	86	277.7	1.01	0.68	1.49
anti-Polio 2	81	225.2	72	232.7	0.97	0.62	1.51
anti-Polio 3	93	642.7	78	494.3	1.30	0.83	2.04

Table 8 **Ratios of GMTs between groups (ACWY_2 and MenCCRM) for anti-Polio 1, anti-Polio 2 and anti-Polio 3, at one month post-primary vaccinations (Primary ATP cohort for immunogenicity)**

					GMT ratio (ACWY_2 / MenCCRM)		
	ACWY_2		MenCCRM			95% CI	
Antibody	N	GMT	N	GMT	Value	LL	UL
anti-Polio 1	83	317.9	90	424.1	0.75	0.49	1.15
anti-Polio 2	71	244.8	81	274.5	0.89	0.57	1.41
anti-Polio 3	79	675.0	87	674.0	1.00	0.67	1.50

Table 9 **Ratios of GMTs between groups (ACWY_2 and MenC-TT) for anti-Polio 1, anti-Polio 2 and anti-Polio 3, at one month post-primary vaccinations (Primary ATP cohort for immunogenicity)**

					GMT ratio (ACWY_2 / MenC-TT)		
	ACWY_2		MenC-TT			95% CI	
Antibody	N	GMT	N	GMT	Value	LL	UL
anti-Polio 1	83	317.9	86	277.7	1.14	0.72	1.82
anti-Polio 2	71	244.8	72	232.7	1.05	0.64	1.74
anti-Polio 3	79	675.0	78	494.3	1.37	0.85	2.20

After the booster dose all GMTs exceeded 900 and all except the GMT in the 3-dose Nimenrix group for poliovirus 1 exceeded 1000. The GMTs were higher in the monovalent MenC groups with the exception of the response to poliovirus 3 in the Nimenrix 2-dose group, which was higher than values in either monovalent MenC group. However, since there was a very clear and profound anamnestic response to IPV in all groups it is not at all likely that the differences observed are clinically important.

Responses to Synflorix

After the primary series the percentages with antibody concentrations ≥0.35 µg/mL was at least 74.0% for all groups and all serotypes. The lowest GMC observed was 0.7 μg/ml (serotype 5 in the ACWY2 group) and the highest was 8.51 μg/ml (serotype 14 in the MenC-CRM197 group). As shown in the table below, antibody concentrations for individual serotypes were generally comparable across the four treatment groups.

Table 13. Number and percentage of subjects with anti-1, anti-4, anti-5, anti- 6B, anti-7F, anti-9V, anti-14, anti-18C, anti-19F and anti-23F antibody concentrations equal to or above 0.15 micrograms per ml and 0.35 micrograms per ml and GMCs (Primary ATP cohort for immunogenicity)

				≥ 0.15 µg/ml				≥ 0.35 µg/ml				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-1	ACWY_3	PRE	98	18	18.4	11.3	27.5	3	3.1	0.6	8.7	0.09	0.08	0.10
		PIII(M3)	96	96	100	96.2	100	93	96.9	91.1	99.4	1.36	1.15	1.62
	ACWY_2	PRE	92	15	16.3	9.4	25.5	9	9.8	4.6	17.8	0.10	0.09	0.12
		PIII(M3)	104	102	98.1	93.2	99.8	95	91.3	84.2	96.0	1.13	0.96	1.34
	MenCCRM	PRE	90	17	18.9	11.4	28.5	8	8.9	3.9	16.8	0.10	0.09	0.12
		PIII(M3)	93	93	100	96.1	100	89	95.7	89.4	98.8	1.26	1.06	1.50
	MenC-TT	PRE	97	18	18.6	11.4	27.7	8	8.2	3.6	15.6	0.10	0.09	0.11
		PIII(M3)	103	103	100	96.5	100	91	88.3	80.5	93.8	1.02	0.88	1.18
anti-4	ACWY_3	PRE	98	11	11.2	5.7	19.2	2	2.0	0.2	7.2	0.09	0.08	0.09
		PIII(M3)	96	96	100	96.2	100	94	97.9	92.7	99.7	1.84	1.58	2.15
	ACWY_2	PRE	93	11	11.8	6.1	20.2	2	2.2	0.3	7.6	0.09	0.08	0.09
		PIII(M3)	104	102	98.1	93.2	99.8	99	95.2	89.1	98.4	1.56	1.31	1.86
	MenCCRM	PRE	92	13	14.1	7.7	23.0	2	2.2	0.3	7.6	0.09	0.08	0.10
		PIII(M3)	95	95	100	96.2	100	93	97.9	92.6	99.7	1.77	1.50	2.10
	MenC-TT	PRE	95	12	12.6	6.7	21.0	1	1.1	0.0	5.7	0.09	0.08	0.09
		PIII(M3)	103	103	100	96.5	100	99	96.1	90.4	98.9	1.60	1.37	1.85
anti-5	ACWY_3	PRE	97	42	43.3	33.3	53.7	10	10.3	5.1	18.1	0.13	0.11	0.15
		PIII(M3)	96	95	99.0	94.3	100	84	87.5	79.2	93.4	0.82	0.71	0.95
	ACWY_2	PRE	92	32	34.8	25.1	45.4	5	5.4	1.8	12.2	0.12	0.10	0.13
		PIII(M3)	104	102	98.1	93.2	99.8	86	82.7	74.0	89.4	0.70	0.61	0.81
	MenCCRM	PRE	91	39	42.9	32.5	53.7	9	9.9	4.6	17.9	0.13	0.11	0.15
		PIII(M3)	93	93	100	96.1	100	80	86.0	77.3	92.3	0.77	0.66	0.89
	MenC-TT	PRE	96	33	34.4	25.0	44.8	14	14.6	8.2	23.3	0.12	0.11	0.15
		PIII(M3)	103	101	98.1	93.2	99.8	92	89.3	81.7	94.5	0.74	0.65	0.85
anti-6B	ACWY_3	PRE	97	55	56.7	46.3	66.7	27	27.8	19.2	37.9	0.18	0.15	0.21
		PIII(M3)	96	88	91.7	84.2	96.3	71	74.0	64.0	82.4	0.79	0.62	1.00
	ACWY_2	PRE	92	42	45.7	35.2	56.4	19	20.7	12.9	30.4	0.15	0.13	0.19
		PIII(M3)	104	95	91.3	84.2	96.0	82	78.8	69.7	86.2	0.90	0.71	1.14
	MenCCRM	PRE	91	41	45.1	34.6	55.8	20	22.0	14.0	31.9	0.15	0.13	0.19
		PIII(M3)	93	88	94.6	87.9	98.2	75	80.6	71.1	88.1	1.08	0.84	1.38
	MenC-TT	PRE	96	50	52.1	41.6	62.4	26	27.1	18.5	37.1	0.18	0.15	0.22
		PIII(M3)	103	90	87.4	79.4	93.1	81	78.6	69.5	86.1	0.86	0.67	1.12
anti-7F	ACWY_3	PRE	98	38	38.8	29.1	49.2	13	13.3	7.3	21.6	0.13	0.11	0.16
		PIII(M3)	96	96	100	96.2	100	94	97.9	92.7	99.7	1.91	1.63	2.23
	ACWY_2	PRE	92	43	46.7	36.3	57.4	18	19.6	12.0	29.1	0.17	0.13	0.21
		PIII(M3)	104	102	98.1	93.2	99.8	99	95.2	89.1	98.4	1.84	1.56	2.18
	MenCCRM	PRE	92	44	47.8	37.3	58.5	20	21.7	13.8	31.6	0.16	0.13	0.20
		PIII(M3)	93	93	100	96.1	100	93	100	96.1	100	2.13	1.82	2.49
	MenC-TT	PRE	96	49	51.0	40.6	61.4	16	16.7	9.8	25.6	0.15	0.13	0.18
		PIII(M3)	103	103	100	96.5	100	103	100	96.5	100	1.87	1.62	2.15
anti-9V	ACWY_3	PRE	97	38	39.2	29.4	49.6	9	9.3	4.3	16.9	0.13	0.11	0.15
		PIII(M3)	96	94	97.9	92.7	99.7	92	95.8	89.7	98.9	1.31	1.10	1.56
	ACWY_2	PRE	93	44	47.3	36.9	57.9	18	19.4	11.9	28.9	0.15	0.13	0.18
		PIII(M3)	104	102	98.1	93.2	99.8	99	95.2	89.1	98.4	1.12	0.97	1.29
	MenCCRM	PRE	92	35	38.0	28.1	48.8	12	13.0	6.9	21.7	0.13	0.11	0.15
		PIII(M3)	93	90	96.8	90.9	99.3	88	94.6	87.9	98.2	1.22	1.02	1.46

				≥ 0.15 µg/ml				≥ 0.35 µg/ml				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
	MenC-TT	PRE	96	43	44.8	34.6	55.3	16	16.7	9.8	25.6	0.14	0.12	0.17
		PIII(M3)	103	103	100	96.5	100	99	96.1	90.4	98.9	1.21	1.07	1.38
anti-14	ACWY_3	PRE	97	72	74.2	64.3	82.6	53	54.6	44.2	64.8	0.50	0.37	0.67
		PIII(M3)	96	96	100	96.2	100	96	100	96.2	100	7.55	6.40	8.90
	ACWY_2	PRE	92	69	75.0	64.9	83.4	57	62.0	51.2	71.9	0.61	0.44	0.85
		PIII(M3)	103	103	100	96.5	100	103	100	96.5	100	7.40	6.35	8.62
	MenCCRM	PRE	90	74	82.2	72.7	89.5	57	63.3	52.5	73.2	0.59	0.44	0.79
		PIII(M3)	95	95	100	96.2	100	95	100	96.2	100	8.51	7.09	10.22
	MenC-TT	PRE	95	80	84.2	75.3	90.9	67	70.5	60.3	79.4	0.74	0.56	0.99
		PIII(M3)	103	103	100	96.5	100	103	100	96.5	100	6.04	5.04	7.24
anti-18C	ACWY_3	PRE	96	30	31.3	22.2	41.5	14	14.6	8.2	23.3	0.13	0.11	0.16
		PIII(M3)	96	96	100	96.2	100	90	93.8	86.9	97.7	2.14	1.74	2.64
	ACWY_2	PRE	93	44	47.3	36.9	57.9	18	19.4	11.9	28.9	0.16	0.13	0.20
		PIII(M3)	103	101	98.1	93.2	99.8	100	97.1	91.7	99.4	1.77	1.47	2.13
	MenCCRM	PRE	91	45	49.5	38.8	60.1	20	22.0	14.0	31.9	0.17	0.14	0.21
		PIII(M3)	94	93	98.9	94.2	100	89	94.7	88.0	98.3	2.39	1.96	2.93
	MenC-TT	PRE	94	43	45.7	35.4	56.3	10	10.6	5.2	18.7	0.14	0.12	0.16
		PIII(M3)	103	103	100	96.5	100	101	98.1	93.2	99.8	2.80	2.40	3.27
anti-19F	ACWY_3	PRE	96	41	42.7	32.7	53.2	21	21.9	14.1	31.5	0.15	0.13	0.19
		PIII(M3)	96	94	97.9	92.7	99.7	92	95.8	89.7	98.9	3.01	2.37	3.82
	ACWY_2	PRE	93	61	65.6	55.0	75.1	30	32.3	22.9	42.7	0.23	0.19	0.28
		PIII(M3)	104	100	96.2	90.4	98.9	94	90.4	83.0	95.3	2.60	2.01	3.35
	MenCCRM	PRE	91	51	56.0	45.2	66.4	27	29.7	20.5	40.2	0.20	0.16	0.25
		PIII(M3)	95	94	98.9	94.3	100	90	94.7	88.1	98.3	2.89	2.26	3.69
	MenC-TT	PRE	96	53	55.2	44.7	65.4	23	24.0	15.8	33.7	0.19	0.15	0.23
		PIII(M3)	103	102	99.0	94.7	100	99	96.1	90.4	98.9	2.85	2.29	3.54
anti-23F	ACWY_3	PRE	97	37	38.1	28.5	48.6	16	16.5	9.7	25.4	0.14	0.11	0.16
		PIII(M3)	95	90	94.7	88.1	98.3	83	87.4	79.0	93.3	0.96	0.78	1.18
	ACWY_2	PRE	92	38	41.3	31.1	52.1	13	14.1	7.7	23.0	0.14	0.11	0.17
		PIII(M3)	104	99	95.2	89.1	98.4	83	79.8	70.8	87.0	0.85	0.69	1.06
	MenCCRM	PRE	90	29	32.2	22.8	42.9	13	14.4	7.9	23.4	0.13	0.11	0.15
		PIII(M3)	94	91	96.8	91.0	99.3	77	81.9	72.6	89.1	1.08	0.86	1.36
	MenC-TT	PRE	96	40	41.7	31.7	52.2	18	18.8	11.5	28.0	0.15	0.12	0.17
		PIII(M3)	103	98	95.1	89.0	98.4	86	83.5	74.9	90.1	0.94	0.77	1.16

Prior to the booster dose there were considerable differences in antibody concentrations between serotypes but, within each serotype, there were no major differences between treatment groups. After the booster dose concentrations ≥0.35 µg/mL were observed for at least 91.1% of subjects against each serotype. The lowest GMC was 0.84 µg/ml (serotype 5 in the MenC-TT group) and the highest was 9.75 µg/ml (serotype 14 in the MenC-CRM197 group). As before, the antibody concentrations for individual serotypes were broadly similar across the four treatment groups.

Total vaccinated cohort analysis

Since the percentage of subjects with serological results excluded from the ATP cohorts (primary and booster phases) was higher than 5%, a second analysis based on the Total Vaccinated Cohorts (TVC) was performed. The exploratory and descriptive results for immunogenicity for the Total Vaccinated Cohorts were consistent with the results for the ATP immunogenicity cohorts for both the primary and booster phases.

The TVC data has been reflected in the SmPC table 2 section 5.1:

Table: Bactericidal antibody responses (rSBA*) and (hSBA) in infants after two doses given 2 months apart and after a booster dose at 12 months of age (Study MenACWY-TT-083)**

Meningococcal Group	Vaccine group		rSBA*			hSBA**		
			N	≥8 (95% CI)	GMT (95% CI)	N	≥8 (95% CI)	GMT (95% CI)
A	Nimenrix	Post dose 2[1]	456	97.4% (95.4; 98.6)	203 (182; 227)	202	96.5% (93.0; 98.6)	157 (131; 188)
		Post booster[1]	462	99.6% (98.4; 99.9)	1561 (1412; 1725)	214	99.5% (97.4;100)	1007 (836;1214)
C	Nimenrix	Post dose 2[1]	456	98.7% (97.2; 99.5)	612 (540; 693)	218	98.6% (96.0; 99.7)	1308 (1052; 1627)
		Post booster[1]	463	99.8% (98.8; 100)	1177 (1059; 1308)	221	99.5% (97.5; 100)	4992 (4086; 6100)
	MenC-CRM vaccine	Post dose 2[1]	455	99.6% (98.4; 99.9)	958 (850; 1079)	202	100% (98.2; 100)	3188 (2646; 3841)
		Post booster[1]	446	98.4% (96.8; 99.4)	1051 (920; 1202)	216	100% (98.3; 100)	5438 (4412; 6702)
	MenC-TT vaccine	Post dose 2[1]	457	100% (99.2; 100)	1188 (1080; 1307)	226	100% (98.4; 100)	2626 (2219; 3109)
		Post booster[1]	459	100% (99.2; 100)	1960 (1776; 2163)	219	100% (98.3; 100)	5542 (4765; 6446)
W	Nimenrix	Post dose 2[1]	455	99.1% (97.8; 99.8)	1605 (1383; 1862)	217	100% (98.3; 100)	753 (644; 882)
		Post booster[1]	462	99.8% (98.8; 100)	2777 (2485; 3104)	218	100% (98.3; 100)	5123 (4504; 5826)
Y	Nimenrix	Post dose 2[1]	456	98.2% (96.6; 99.2)	483 (419; 558)	214	97.7% (94.6; 99.2)	328 (276; 390)
		Post booster[1]	462	99.4% (99.1; 99.9)	881 (787; 986)	217	100% (98.3; 100)	2954 (2498; 3493)

The analysis of immunogenicity was conducted on the primary according-to-protocol (ATP) cohort for immunogenicity.

*rSBA testing performed at Public Health England (PHE) laboratories in UK

**hSBA tested at GSK laboratories

[1] blood sampling performed 21 to 48 days post vaccination

2.4.1.2. Additional data

Data related to the age of the indication

The MAH seeks approval from 6 weeks of age, however the mean age of the subjects in the primary ATP cohort for immunogenicity was 8.7 weeks and the median was 9 weeks and infants had to have been born after at least 36 weeks gestation. The MAH was therefore requested during the procedure to present the numbers of infants who were actually 6-8 weeks old at the time of the first dose and to provide the immune responses to meningococcal antigens for those aged <8 weeks and >8 weeks at enrolment.

The protocol stipulated that eligible subjects were to be between 6 and 12 weeks (42-90 days) old at the time of the first vaccination. The demographic characteristics of infants aged 6 to 8 weeks and >8 weeks at the time of first dose for the primary analysis according to protocol (ATP) cohort showed that overall the distribution of infants between the two age groups was balanced, with 869 infants (47.2%) 6 to 8 weeks of age and 972 infants (52.8%) >8 weeks of age. Similar female:male distributions were seen in the ≤8 weeks group (433 females and 436 males; 49.8% and 50.2%, respectively) and the >8 weeks group (479 females and 493 males; 49.3% and 50.7%, respectively). These similar distributions for infants 6 to 8 weeks and >8 weeks are seen in each of the vaccine groups.

At the 1-month post-primary vaccination series time point (1 month after the last priming dose [PIII(M3)] in Table 14), in both the 2-dose and the 3-dose MenACWY-TT groups, the percentage of subjects achieving rSBA titres of ≥1:8 and ≥1:128 were similar between the 6 to 8 weeks and the >8 weeks age groups for all meningococcal serogroups (Table 14).

At the same time point and for the 2-dose and 3-dose regimens, the percentage of subjects achieving hSBA titres ≥1:4 and ≥1:8 were similar between the 6 to 8 weeks and the >8 weeks age groups for all serogroups (not shown in this report).

There are some instances for rSBA suggesting slightly lower responses in the younger cohort but these become apparent only at the upper titre cut-off. This pattern was not seen with the hSBA data.

Table 14. Number and Percentage of Subjects With rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY Antibody Titer Equal to or Above 1:8 and 1:128 and GMTs by Age Group (Primary ATP Cohort for Immunogenicity) (Study MENACWY-TT-083)

				≥ 1:8					≥ 1:128				GMT		
							95% CI				95% CI			95% CI	
Antibody	Group	Age Group	Timing	N	n	%	LL	UL	n	%	LL	UL	Value	LL	UL
rSBA-MenA	ACWY_3	≤ 8 weeks	PRE	106	1	0.9	0.0	5.1	1	0.9	0.0	5.1	4.1	3.9	4.4
			PIII(M3)	203	201	99.0	96.5	99.9	172	84.7	79.0	89.4	220.3	191.8	253.1
		> 8 weeks	PRE	117	1	0.9	0.0	4.7	0	0.0	0.0	3.1	4.0	4.0	4.1
			PIII(M3)	259	258	99.6	97.9	100.0	230	88.8	84.3	92.4	277.4	245.5	313.5
	ACWY_2	≤ 8 weeks	PRE	102	2	2.0	0.2	6.9	0	0.0	0.0	3.6	4.1	3.9	4.3
			PIII(M3)	226	218	96.5	93.1	98.5	179	79.2	73.3	84.3	183.3	154.8	216.9
		> 8 weeks	PRE	117	2	1.7	0.2	6.0	0	0.0	0.0	3.1	4.1	3.9	4.3
			PIII(M3)	230	226	98.3	95.6	99.5	195	84.8	79.5	89.2	225.6	194.9	261.0
	MenCCRM	≤ 8 weeks	PRE	48	2	4.2	0.5	14.3	0	0.0	0.0	7.4	4.2	3.9	4.6
			PIII(M3)	218	2	0.9	0.1	3.3	1	0.5	0.0	2.5	4.1	3.9	4.2
		> 8 weeks	PRE	49	0	0.0	0.0	7.3	0	0.0	0.0	7.3	4.0	NE	NE
			PIII(M3)	237	4	1.7	0.5	4.3	2	0.8	0.1	3.0	4.2	4.0	4.4
	MenC-TT	≤ 8 weeks	PRE	52	2	3.8	0.5	13.2	0	0.0	0.0	6.8	4.3	3.9	4.7
			PIII(M3)	217	3	1.4	0.3	4.0	1	0.5	0.0	2.5	4.1	4.0	4.3
		> 8 weeks	PRE	58	0	0.0	0.0	6.2	0	0.0	0.0	6.2	4.0	NE	NE
			PIII(M3)	240	0	0.0	0.0	1.5	0	0.0	0.0	1.5	4.0	NE	NE
rSBA-MenC	ACWY_3	≤ 8 weeks	PRE	106	6	5.7	2.1	11.9	0	0.0	0.0	3.4	4.4	4.0	4.7
			PIII(M3)	202	200	99.0	96.5	99.9	188	93.1	88.6	96.2	369.6	316.7	431.3
		> 8 weeks	PRE	117	6	5.1	1.9	10.8	2	1.7	0.2	6.0	4.5	4.0	5.1
			PIII(M3)	259	259	100.0	98.6	100.0	237	91.5	87.4	94.6	421.1	366.0	484.6
	ACWY_2	≤ 8 weeks	PRE	102	6	5.9	2.2	12.4	0	0.0	0.0	3.6	4.3	4.0	4.6
			PIII(M3)	226	223	98.7	96.2	99.7	211	93.4	89.3	96.2	534.5	447.7	638.0
		> 8 weeks	PRE	118	4	3.4	0.9	8.5	1	0.8	0.0	4.6	4.2	4.0	4.5
			PIII(M3)	230	227	98.7	96.2	99.7	217	94.3	90.5	97.0	698.4	586.0	832.3

Table 14. Number and Percentage of Subjects With rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY Antibody Titer Equal to or Above 1:8 and 1:128 and GMTs by Age Group (Primary ATP Cohort for Immunogenicity) (Study MENACWY-TT-083)

				≥ 1:8					≥ 1:128				GMT		
							95% CI				95% CI			95% CI	
Antibody	Group	Age Group	Timing	N	n	%	LL	UL	n	%	LL	UL	Value	LL	UL
	MenCCRM	≤ 8 weeks	PRE	100	10	10.0	4.9	17.6	3	3.0	0.6	8.5	5.1	4.3	6.1
			PIII(M3)	217	216	99.5	97.5	100.0	209	96.3	92.9	98.4	859.0	727.4	1014.5
		> 8 weeks	PRE	107	5	4.7	1.5	10.6	3	2.8	0.6	8.0	4.7	4.0	5.5
			PIII(M3)	238	237	99.6	97.7	100.0	228	95.8	92.4	98.0	1057.3	892.4	1252.8
	MenC-TT	≤ 8 weeks	PRE	101	6	5.9	2.2	12.5	1	1.0	0.0	5.4	4.6	4.1	5.2
			PIII(M3)	217	217	100.0	98.3	100.0	217	100.0	98.3	100.0	1119.8	989.5	1267.3
		> 8 weeks	PRE	119	8	6.7	2.9	12.8	4	3.4	0.9	8.4	4.9	4.2	5.7
			PIII(M3)	240	240	100.0	98.5	100.0	239	99.6	97.7	100.0	1253.4	1086.6	1445.9
rSBA-MenW-135	ACWY_3	≤ 8 weeks	PRE	86	2	2.3	0.3	8.1	0	0.0	0.0	4.2	4.1	4.0	4.2
			PIII(M3)	203	201	99.0	96.5	99.9	186	91.6	86.9	95.0	1006.7	806.2	1257.0
		> 8 weeks	PRE	129	6	4.7	1.7	9.8	0	0.0	0.0	2.8	4.4	4.1	4.7
			PIII(M3)	258	256	99.2	97.2	99.9	248	96.1	93.0	98.1	1219.4	1028.4	1445.8
	ACWY_2	≤ 8 weeks	PRE	112	8	7.1	3.1	13.6	0	0.0	0.0	3.2	4.4	4.1	4.8
			PIII(M3)	226	224	99.1	96.8	99.9	215	95.1	91.5	97.5	1592.6	1282.3	1978.0
		> 8 weeks	PRE	105	4	3.8	1.0	9.5	1	1.0	0.0	5.2	4.3	4.0	4.6
			PIII(M3)	229	227	99.1	96.9	99.9	220	96.1	92.7	98.2	1617.3	1317.0	1986.2
	MenCCRM	≤ 8 weeks	PRE	48	2	4.2	0.5	14.3	1	2.1	0.1	11.1	4.5	3.7	5.5
			PIII(M3)	216	6	2.8	1.0	5.9	5	2.3	0.8	5.3	4.5	4.1	5.0
		> 8 weeks	PRE	62	3	4.8	1.0	13.5	0	0.0	0.0	5.8	4.2	4.0	4.5
			PIII(M3)	237	3	1.3	0.3	3.7	3	1.3	0.3	3.7	4.3	3.9	4.7
	MenC-TT	≤ 8 weeks	PRE	56	3	5.4	1.1	14.9	1	1.8	0.0	9.6	4.5	3.8	5.4
			PIII(M3)	216	5	2.3	0.8	5.3	3	1.4	0.3	4.0	4.4	4.0	4.9
		> 8 weeks	PRE	51	0	0.0	0.0	7.0	0	0.0	0.0	7.0	4.0	NE	NE
			PIII(M3)	239	3	1.3	0.3	3.6	1	0.4	0.0	2.3	4.1	4.0	4.2
rSBA-MenY	ACWY_3	≤ 8 weeks	PRE	86	2	2.3	0.3	8.1	0	0.0	0.0	4.2	4.2	3.9	4.5
			PIII(M3)	202	189	93.6	89.2	96.5	160	79.2	73.0	84.6	260.4	202.1	335.6

Table 14. Number and Percentage of Subjects With rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY Antibody Titer Equal to or Above 1:8 and 1:128 and GMTs by Age Group (Primary ATP Cohort for Immunogenicity) (Study MENACWY-TT-083)

				≥ 1:8					≥ 1:128				GMT		
							95% CI				95% CI			95% CI	
Antibody	Group	Age Group	Timing	N	n	%	LL	UL	n	%	LL	UL	Value	LL	UL
		> 8 weeks	PRE	129	4	3.1	0.9	7.7	0	0.0	0.0	2.8	4.2	4.0	4.4
			PIII(M3)	259	240	92.7	88.8	95.5	211	81.5	76.2	86.0	267.9	215.9	332.4
	ACWY_2	≤ 8 weeks	PRE	114	3	2.6	0.5	7.5	3	2.6	0.5	7.5	4.4	3.9	4.9
			PIII(M3)	226	221	97.8	94.9	99.3	202	89.4	84.6	93.1	452.9	365.9	560.6
		> 8 weeks	PRE	105	3	2.9	0.6	8.1	0	0.0	0.0	3.5	4.1	4.0	4.2
			PIII(M3)	230	227	98.7	96.2	99.7	205	89.1	84.4	92.8	515.1	424.1	625.6
	MenCCRM	≤ 8 weeks	PRE	48	5	10.4	3.5	22.7	1	2.1	0.1	11.1	5.0	4.0	6.1
			PIII(M3)	218	9	4.1	1.9	7.7	7	3.2	1.3	6.5	4.6	4.2	5.1
		> 8 weeks	PRE	63	3	4.8	1.0	13.3	0	0.0	0.0	5.7	4.5	3.9	5.1
			PIII(M3)	237	2	0.8	0.1	3.0	2	0.8	0.1	3.0	4.1	3.9	4.3
	MenC-TT	≤ 8 weeks	PRE	56	2	3.6	0.4	12.3	0	0.0	0.0	6.4	4.2	3.9	4.5
			PIII(M3)	217	7	3.2	1.3	6.5	6	2.8	1.0	5.9	4.5	4.1	4.9
		> 8 weeks	PRE	51	1	2.0	0.0	10.4	1	2.0	0.0	10.4	4.3	3.7	4.9
			PIII(M3)	240	7	2.9	1.2	5.9	7	2.9	1.2	5.9	4.6	4.1	5.0

Age group is defined by subject's age at first vaccination visit.

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 titer calculated on all subjects.

N = number of subjects with available results.

n/% = number/percentage of subjects with titer 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.

NE = not estimable.

Table 14. Number and Percentage of Subjects With rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY Antibody Titer Equal to or Above 1:8 and 1:128 and GMTs by Age Group (Primary ATP Cohort for Immunogenicity) (Study MENACWY-TT-083)

				≥ 1:8					≥ 1:128				GMT		
							95% CI				95% CI			95% CI	
Antibody	Group	Age Group	Timing	N	n	%	LL	UL	n	%	LL	UL	Value	LL	UL

Assay performance

During the procedure the MAH was asked to discuss changes in sensitivity with the rSBA and hSBA used in the initial Nimenrix application and the assays used in this extension of indication (assay results were higher with rSBA vs. hSBA in the MAA but the opposite was seen in the current application). The MAH clarified that for post-licensure studies (including Study MenACWY-TT-083) the Company switched from the GSK rSBA to the Public Health England (PHE) rSBA assay at the end of 2011. The GSK and PHE rSBA assays have different levels of sensitivity. Titres measured with the PHE rSBA are generally lower than those obtained with the GSK assays used at the time of licensure of Nimenrix. This is especially true for pre vaccination (baseline) sera.

It was clarified that there were no changes in assay procedure or conditions during testing, except for routine changes in qualified lots of complement and bacteria to replace lots that became consumed. Assay performance during the testing of serum samples from Study MenACWY-TT-083 was monitored routinely via quality control sample (QCS) titres, which did not reveal a shift or drift in assay performance over the period spanning MenACWY-TT-083 testing. Based on the data submitted using either assay it is clear that there is a marked immune response to Nimenrix, that it is not substantially improved by giving 3 vs. 2 doses, that immune responses to MenA, W-135 and Y are much higher in the Nimenrix group, whilst GMTs for MenC are higher with the monovalent vaccines.

Additionally the MAH was also asked to provide rSBA and hSBA assay performance data generated at PHE and GSK, respectively, during the testing of sera from studies submitted with the initial MAA. These data did not indicate any shifts in sensitivity of either assay.

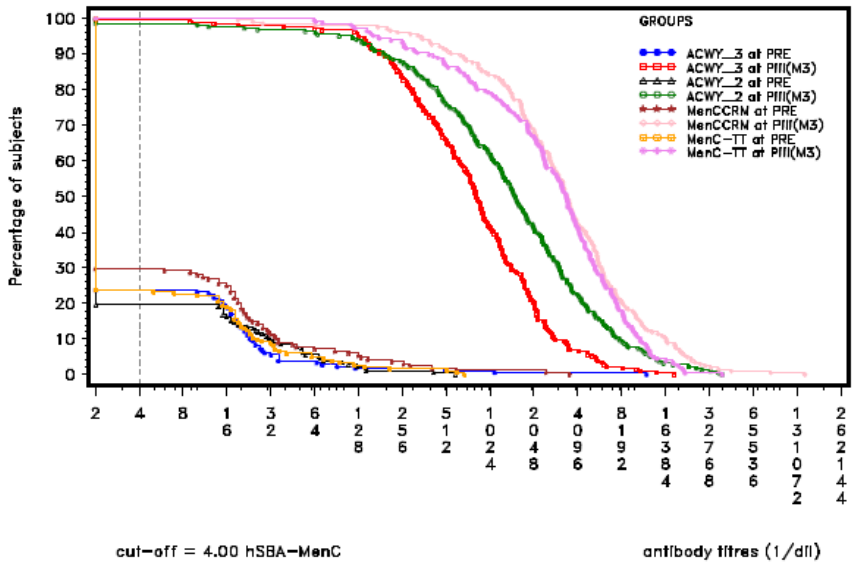
Data on GMTs for Meningococcal serogroup C in Nimenrix vs. control groups

It was observed that one month post-primary vaccination rSBA-MenC and hSBA MenC geometric mean titres (GMTs) are lower in the MenACWY-TT groups compared to the control vaccines. The clinical significance of this difference in GMTs is not known. The clinically relevant endpoint is rather the percentage of subjects with MenC titers equal to or above the seroprotective level (>1:8) one month post primary vaccination.

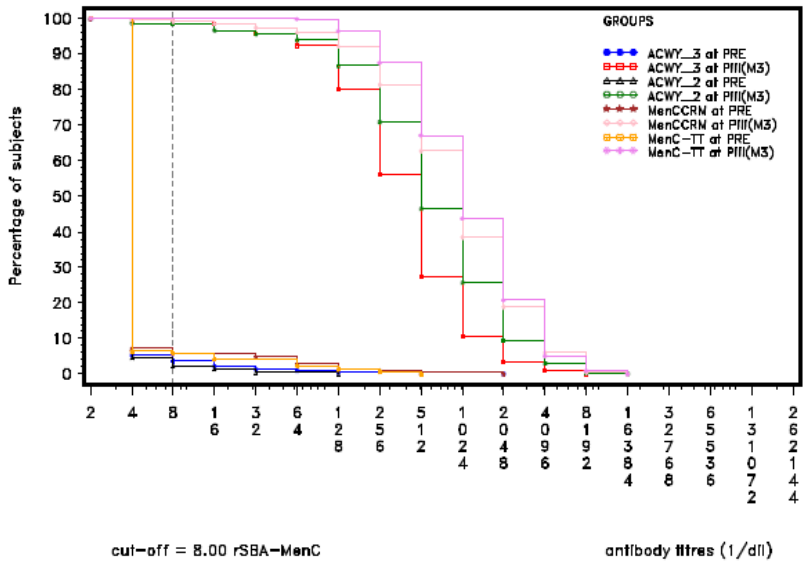
As can be seen in Table 5 and Table 6, respectively, the percentage of subjects with rSBA-MenC and hSBA-MenC titers >1:8 one month after the primary vaccination [time point PIII(M3)] are similar between MenACWY-TT and the control vaccines (>98.6% of subjects with titres >1:8 for rSBA and hSBA). The same holds true for both the pre-booster and post-booster time points [PIII(M10) and PIV(M11) in Table 5 and Table 6. This observation suggests that the protection against MenC provided by MenACWY-TT can be expected to be similar to that provided by both Menjugate and NeisVac-C in infants and toddlers.

Using the PHE assay, prior evaluations using MenC serological data and vaccine effectiveness data support the utility of looking at percentages with titres at least 1:8 but also at percentages reaching higher thresholds (e.g. at least 1:64 post-primary). Nevertheless, the reverse cumulative distribution curves for post-primary rSBA and hSBA titres (shown below) do not diverge (i.e. in that no group falls below 90% reaching that threshold) until titres higher than ~128-256. These curves support a conclusion that the differences in GMTs are not very likely to have clinical significance.

Reverse cumulative distribution curve for hSBA-MenC antibody titres at pre- and post-primary vaccinations (Primary ATP cohort for immunogenicity)



Reverse cumulative distribution curve for rSBA-MenC antibody titres at pre- and post-primary vaccinations (Primary ATP cohort for immunogenicity)



2.4.1.3. Summary of study MenACWY-TT-083

The following table summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 15. Summary of Efficacy for trial MenACWY-TT-083

Title: MenACWY-TT-083		
Design	Randomised controlled open label trial to compare two schedules of Nimenrix in infancy with MenC-CRM197 and with MenC-TT	
	Duration of main phase:	July 2010 to September 2013

Hypothesis	Non-inferiority for rSBA MenC for Nimenrix vs. control monovalent MenCCs		
Treatment groups	Nimenrix		2, 4 and 12 months 2, 3, 4 and 12 months
	MenC-CRM197		2, 4 and 12 months
	MenC-TT		2, 4 and 12 months
Endpoints and definitions	rSBA MenC at age 5 months rSBA MenA, W, Y at age 5 months	Nimenrix vs. MenC-CRM197 and vs. MenC-TT % with rSBA to each ≥1:8	Each set of 3 primary objectives repeated for 2-dose and 3-dose schedules of Nimenrix Lower bounds of 95% CI around percentage were to be at least 80% for each group
	rSBA pre-/post-boost hSBA (subset) Immune response to Infanrix hexa and to Synflorix	All groups received same background vaccinations	Immune responses to concomitant antigens based on the usual criteria; no control group (without any MenCC vaccine)

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	ATP immunogenicity population at 5 months of age (one month after the second or third dose)			
Descriptive statistics and estimate variability at 5 months of age	Nimenrix 2 dose	Nimenrix 3 dose	MenC-CRM197	MenC-TT
	TVC 524	528	516	527
	MenC ≥1:8 98.7% NI vs. controls	99.6% NI vs. controls	99.6%	100%
	MenA ≥1:8 97.4%	99.4%	1.3%	0.7%
	MenW ≥1:8 99.1%	99.1%	2%	1.8%
	MenY ≥1:8 98.2%	93.1%	2.4%	3.1%
Notes	Percentages with rSBA titres ≥1:128 and GMTs mostly suggested a possible benefit for 2 vs. 3 doses Nimenrix The subset hSBA data generally followed the rSBA pattern			
Analysis description	**Secondary analysis - Post-booster responses**			
Descriptive statistics and estimate variability	Nimenrix 2 dose	Nimenrix 3 dose	MenC-CRM197	MenC-TT
	MenC ≥1:8 99.8% NI vs. controls	99.5% NI vs. controls	98.4%	100%
	MenA ≥1:8 99.6%	99.5%	4.7%	4.1%
	MenW ≥1:8 99.8%	99.1%	7.6%	8.1%
	MenY ≥1:8 99.4%	99.3%	10.1%	8.7%

Notes	Post-boost GMTs demonstrated anamnestic responses to MenACWY-TT No indication of important differences in co-administration effects for Nimenrix vs. monovalent MenCC vaccines except for the expected effects reflecting the conjugating proteins The subset hSBA data followed the rSBA data in pattern of responses

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The study was of adequate design and conduct. It was of necessity open label but the primary endpoints are laboratory readouts and these were produced by staff unaware of the treatment assignment. Given the age of the subjects and volumes of blood needed, it is acceptable that assays were conducted in randomly selected subsets.

Although enrolment was predominant in Spain, the data by country indicated comparable patterns of responses between Spain and Germany. There are too few subjects from Estonia to comment. In accordance with the countries that participated in the study, in which there has not been widespread vaccination of women now of child-bearing age against meningococcal serogroups A, C, W or Y, the pre-vaccination titres in infants were very low. In the UK, where there was a large catch-up programme at the time of introduction of MenC vaccination, a substantial proportion of women now giving birth may have been primed with a MenC conjugate. Nevertheless, their circulating antibody is likely to be low, so that infant levels are not expected to be at a level that could interfere with the infant immune response.

Minimum age for use

The MAH seeks approval from 6 weeks of age. The mean age of the subjects in the primary ATP cohort for immunogenicity was 8.7 weeks and the median was 9 weeks and infants had to have been born after at least 36 weeks gestation. The demographic characteristics of infants aged 6 to 8 weeks and >8 weeks at the time of first dose for the primary analysis according to protocol (ATP) cohort showed that overall the distribution of infants between the two age groups was balanced, with 869 infants (47.2%) 6 to 8 weeks of age and 972 infants (52.8%) >8 weeks of age. At 1-month after the last priming dose [PIII(M3)] in Table 14), in both the 2-dose and the 3-dose MenACWY-TT groups, the percentage of subjects achieving rSBA titres of ≥1:8 and ≥1:128 were similar between the 6 to 8 weeks and the >8 weeks age groups for all meningococcal serogroups (similar results with hSBA at titres ≥1:4 and ≥1:8).

The data indicate a good spread of ages and the rSBA and hSBA results support the use of 2 doses even in infants aged 6-< 8 weeks at the time of the first dose.

Immune responses to meningococcal polysaccharides

This study met all six of the pre-defined elements of the primary analysis, which was conducted in a hierarchical fashion. It is noted that the comparisons of percentages achieving the pre-defined titres were based on a non-inferiority margin of 5% in each case. In light of the anticipated high titres and the life-threatening nature of the disease to be prevented, this margin is acceptable. In the primary series the rSBA data indicated at least comparable responses to MenC between either 2 or 3 doses of MenACWY-TT and the two monovalent MenC conjugates. In addition, the data showed that the lower bounds of the 95% CI around the differences in percentages with MenC rSBA titres ≥1:8 were actually within -4%.

Only at the higher cut-offs, reflecting the differences in GMTs, was there a possible advantage for the monovalent MenC vaccines. Even then, >90% in the MenACWY groups had rSBA titres ≥1:128. Some of the findings suggested that 2 doses of MenACWY might actually be better than 3 doses. For example,

rSBA GMTs for MenC were significantly lower for the 3-dose group compared to the other three groups (95% CI did not overlap).

In addition, the rSBA responses to MenA, W and Y did not suggest an advantage for 3 vs. 2 doses of MenACWY-TT. In each case very high percentages in both groups had rSBA titres ≥1:8 at M3 of the study (i.e. at about 5 months of age). The lower confidence interval limits around the percentages with rSBA titres ≥1:8 were >80% for each meningococcal serogroup. This finding also applied to percentages with titres ≥1:128 except for MenY in the 3-dose group (76.6%) and MenA in the 2-dose group (78.2%).

Although the study was not powered for the comparison of hSBA data (as measured by GSK) between groups, there was a very similar pattern of between-group comparisons as described for the rSBA data (as measured by PHE) for each meningococcal serogroup at M3 of the study. The hSBA data demonstrated a greater advantage for 2 vs. 3 doses of MenACWY-TT than the rSBA data.

The hSBA titres at M3 also showed that the advantage of monovalent MenC conjugates was evident only at the upper titre cut-offs, again reflecting the GMTs. As for the rSBA data, it seems unlikely that the differences observed are clinically important given that > 90% who received MenACWY-TT had hSBA titres ≥1:8.

Before and after the booster dose the rSBA titres were generally comparable between the 2-dose and 3-dose MenACWY-TT groups. Exceptions were higher GMTs for MenW and MenY in the 2-dose vs. 3-dose group with non-overlapping 95% CI. Comparisons with the monovalent MenC groups showed similar proportions with pre- and post-boost titres ≥1:8 and ≥1:128 across the four groups with lower 95% CI within -4%.

The post-boost GMTs for MenC rSBA were similar for the two MenACWY-TT and MenC-CRM197 groups but lower for all 3 vs. MenC-TT with 95% CI that did not overlap. In the two MenACWY-TT groups all post-boost GMTs were higher than the post-primary GMTs, supporting the existence of anamnestic responses to the final dose.

The pre- and post-boost hSBA data showed a comparable pattern of post-boost responses vs. rSBA and further demonstrated anamnestic immune responses to the final dose of MenACWY-TT.

Immune responses to co-administered antigens

In the CHMP scientific advice of 2013 the MAH (GSK) asked about omitting documentation of immune responses to co-administered vaccines. The MAH was advised that in the absence of such data the SmPC would have to carefully clarify that all information on co-administration came from subjects at least 12 months old. Therefore, although lack of such data would not per se preclude an approval for use of Nimenrix in infancy, it would likely severely limit the use of the vaccine at routine immunisation programme visits.

In response, the MAH decided to conduct assays of immune responses to co-administered antigens. Since this was performed for a representative sample from each treatment group, the data allow for an assessment of any impact of MenACWY-TT compared to MenC-CRM197 or MenC-TT. In addition, since all the data on immune responses to meningococcal antigens were obtained against the same background of co-administered vaccines, concluding that responses to MenACWY-TT are satisfactory automatically implies that it may be given with DTaP-IPV-HBV-PRP-T and with Synflorix. Such data cannot be used to support co-administration of MenACWY-TT with PRP-CRM197 or PRP-D constructs or with Prevenar13 in infancy. With regard to the actual immune responses to co-administered antigens:

- The post-primary and post-boost anti-D and anti-TT antibody concentrations were satisfactory and GMCs showed the expected effects of the conjugates co-administered.

- Whilst there is no ICP applicable to pertussis there were no marked differences in antibody to PT, FHA or PRN between treatment groups.
- The post-primary antibody results demonstrate no disadvantages for the Nimenrix groups in terms of percentages reaching titres 1:8 to any of the 3 polioviruses. After the booster dose all subjects in all vaccine groups who were tested had titres of at least 1:8 for each poliovirus. Antibody concentrations data showed no major differences.
- There were no important differences between the four treatment groups for the post-primary, pre-boost or post-boost anti-HBsAg antibody concentrations.
- Differences in the anti-PRP responses emerged for percentages with anti-PRP antibody concentration ≥1.0 μg/ml and the GMCs such that the lowest response was seen in the MenC-CRM197 group after the primary doses. This effect of the type of MenC conjugate has been noted before in studies in which PRP-T has been given to young infants with different MenC conjugates. However, this pattern disappeared after the booster dose when GMCs were numerically lower for the MenACWY-TT groups but almost all subjects achieved ≥1.0 μg/ml anti-PRP concentration.
- Responses to Synflorix, in which 8/10 serotypes are conjugated to Protein D, one to DT (19F) and one to TT (18C), showed the expected variability in immune responses by serotype. The lowest post-primary responses were to serotypes 5 and 6B and the highest to serotype 14. However, for each serotype there were no marked differences in responses between the four treatment groups. There were no OPA data generated so it is not known whether the serotype-specific difference noted in older children (see the SmPC) would also occur in infancy. After the booster dose, concentrations ≥0.35 µg/mL were observed for at least 91.1% of subjects against each serotype. The lowest GMC was 0.84 μg/ml (serotype 5 in the MenC-TT group) and the highest was 9.75 μg/ml (serotype 14 in the MenC-CRM197 group). As before, the antibody concentrations for individual serotypes were broadly similar across the four treatment groups.

2.4.3. Conclusions on clinical efficacy

In summary, the data support use of Nimenrix from 6 weeks of age.

There is no advantage for 3 vs. 2 doses of MenACWY-TT in infants and the 2-dose regimen, with at least 8 weeks between doses, is acceptable. Experience has already demonstrated that a booster dose of MenC is needed. It is very reasonable to assume that this also applies to the other meningococcal serogroups. Immune responses at M12 are clearly anamnestic and can be expected to prolong protection. As in older age groups, for whom a single dose is currently recommended, the need for further doses later in life is not yet fully established. However, long term antibody persistence data for MenC suggest that there could be a benefit from an additional dose(s) after several years have elapsed. This may apply particularly to those who were at the younger end of the age range (e.g. < 5 years old) when first vaccinated. For the present, the SmPC should recommend a booster dose of Nimenrix at 12 months of age.

In infants, Nimenrix can be given concomitantly with combined DTaP-HBV-IPV/Hib vaccines and with 10-valent pneumococcal conjugate vaccine.

2.5. Clinical safety

Introduction

Prior to this variation, the safety profile of Nimenrix in the existing indication was based on a pooled analysis on 9,621 subjects who have been vaccinated with one dose of Nimenrix in clinical studies. This

pooled analysis includes data for 3,079 toddlers (12 months to 23 months), 909 children between 2 and 5 years of age, 990 children between 6 and 10 years of age, 2,317 adolescents (11 to 17 years) and 2,326 adults (18 to 55 years).

In all age groups the most frequently reported local adverse reactions after vaccination were pain (24.1% to 41.3%), redness (15.5% to 35.6%) and swelling (11.3% to 19.9%).

In the 12-23 months and 2-5 years age groups, the most frequently reported general adverse reactions after vaccination were irritability (44.0% and 9.2% respectively), drowsiness (34.1% and 10.8% respectively), loss of appetite (26.6% and 8.2% respectively) and fever (17.1% and 8.1% respectively). In the 12-14 months age group who received 2 doses of Nimenrix given 2 months apart, the first and second doses were associated with similar local and systemic reactogenicity.

In the 6-10, 11-17 and ≥ 18 years age groups, the most frequently reported general adverse reactions after vaccination were headache (15.7%, 22.0% and 21.5% respectively), fatigue (15.6%, 21.9% and 20.7% respectively), gastrointestinal symptoms (9.3%, 9.4% and 8.3% respectively) and fever (8.0%, 5.3% and 4.9% respectively).

In a separate study a single dose of Nimenrix was administered to 274 individuals aged 56 years and older. All adverse reactions reported in this study were already observed in younger age groups.

Study MenACWY-TT-083

See the description of the study design in section 2.4.1. The collection and analysis of the safety data, including the solicited symptoms collected and the grading of AEs, was in accordance with all other vaccine studies conducted by GSK in this age group.

Patient exposure

A total of 2095 subjects were enrolled and vaccinated in the study, of which 1052 subjects received at least 1 dose of MenACWY-TT (Table 16); 2017 subjects received a booster vaccination, of which 1008 subjects received MenACWY-TT. Overall, 3601 doses of MenACWY-TT were administered.

Table 16. Number of subjects who received at least 1 dose of MenACWY-TT vaccine or control vaccines and total number of doses administered

Vaccine	MenACWY-TT		MenC-CRM$_{197}$	MenC-TT
Study group	ACWY_3	ACWY_2	MenC-CRM	MenC-TT
Nber of subjects who received at least 1 dose	528	524	516	527
Nber of doses administered (primary TVC)	1552	1041	1025	1038
Nber of doses administered (booster TVC)	497	511	503	506
Nber of doses administered	2049	1552	1528	1544

Data source: MenACWY-TT-083 (113369) Main Report (11 September 2015) Tables 361 and 406
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
MenC-CRM = 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
Nber = number

The study groups were balanced in terms of demographic characteristics (see section 2.4.1). In the primary TVC, the mean age at the first vaccination dose was 8.6 weeks, the ratio of female/male showed a good balance and was close to 1 (0.99), and the majority of subjects were from White - Caucasian / European heritage (94.4%).

Adverse events

AEs in the primary phase

In the primary phase of the study at least 96.8% of subjects in each treatment group received all their assigned doses of study vaccines.

During the 8-day follow-up period, almost all subjects had at least one symptom (solicited or unsolicited; most of which occurred within 4 days and were considered to be vaccine-related) and about one third had at least one Grade 3 symptom. Reporting rates were similar or slightly lower with sequential doses.

Redness was the most frequently reported solicited local symptom in all four groups during the 8-day post-vaccination period followed by pain and swelling.

Table 17. Incidence of solicited local symptoms reported during the 8-days (Days 0-7) post-vaccination period following each dose and overall (Primary Total Vaccinated cohort)

		ACWY_3					ACWY_2					MenCCRM					MenC-TT				
					95 % CI					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Overall/dose																					
Pain	All	1534	627	40.9	38.4	43.4	1557	633	40.7	38.2	43.1	1525	653	42.8	40.3	45.3	1538	640	41.6	39.1	44.1
	Grade 3	1534	68	4.4	3.5	5.6	1557	88	5.7	4.6	6.9	1525	66	4.3	3.4	5.5	1538	85	5.5	4.4	6.8
	Medical advice	1534	1	0.1	0.0	0.4	1557	6	0.4	0.1	0.8	1525	4	0.3	0.1	0.7	1538	1	0.1	0.0	0.4
Redness (mm)	All	1534	749	48.8	46.3	51.4	1557	765	49.1	46.6	51.6	1525	827	54.2	51.7	56.8	1538	788	51.2	48.7	53.8
	>30	1534	21	1.4	0.8	2.1	1557	16	1.0	0.6	1.7	1525	32	2.1	1.4	2.9	1538	16	1.0	0.6	1.7
	Medical advice	1534	0	0.0	0.0	0.2	1557	4	0.3	0.1	0.7	1525	4	0.3	0.1	0.7	1538	3	0.2	0.0	0.6
Swelling (mm)	All	1534	609	39.7	37.2	42.2	1557	604	38.8	36.4	41.3	1525	656	43.0	40.5	45.5	1538	616	40.1	37.6	42.6
	>30	1534	17	1.1	0.6	1.8	1557	16	1.0	0.6	1.7	1525	39	2.6	1.8	3.5	1538	29	1.9	1.3	2.7
	Medical advice	1534	2	0.1	0.0	0.5	1557	4	0.3	0.1	0.7	1525	4	0.3	0.1	0.7	1538	2	0.1	0.0	0.5
Overall/subject																					
Pain	All	518	319	61.6	57.2	65.8	523	332	63.5	59.2	67.6	509	344	67.6	63.3	71.6	518	327	63.1	58.8	67.3
	Grade 3	518	54	10.4	7.9	13.4	523	67	12.8	10.1	16.0	509	48	9.4	7.0	12.3	518	69	13.3	10.5	16.6
	Medical advice	518	1	0.2	0.0	1.1	523	6	1.1	0.4	2.5	509	4	0.8	0.2	2.0	518	1	0.2	0.0	1.1
Redness (mm)	All	518	363	70.1	65.9	74.0	523	369	70.6	66.4	74.4	509	391	76.8	72.9	80.4	518	371	71.6	67.5	75.5
	>30	518	18	3.5	2.1	5.4	523	15	2.9	1.6	4.7	509	24	4.7	3.0	6.9	518	15	2.9	1.6	4.7
	Medical advice	518	0	0.0	0.0	0.7	523	4	0.8	0.2	1.9	509	4	0.8	0.2	2.0	518	3	0.6	0.1	1.7
Swelling (mm)	All	518	326	62.9	58.6	67.1	523	318	60.8	56.5	65.0	509	343	67.4	63.1	71.4	518	317	61.2	56.8	65.4
	>30	518	15	2.9	1.6	4.7	523	11	2.1	1.1	3.7	509	27	5.3	3.5	7.6	518	24	4.6	3.0	6.8
	Medical advice	518	2	0.4	0.0	1.4	523	4	0.8	0.2	1.9	509	4	0.8	0.2	2.0	518	2	0.4	0.0	1.4

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
For each dose and overall/subject:
N = number of subjects with at least one documented dose
n/%= number/percentage of subjects reporting the symptom at least once
For Overall/dose:
N = number of documented doses
n/%= number/percentage of doses followed by at least one type of symptom
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

(from table 370 – Module 5.3.5.1 study report body)

The data shown by individual vaccine indicated that the meningococcal vaccine sites were least likely to be associated with local symptoms and the Infanrix hexa sites were more likely than the Synflorix sites to be associated with redness and selling.

Irritability was the most frequently reported (in >80% of subjects) solicited general symptom in all four groups during the 8-day post-vaccination period. Grade 3 irritability was reported in about one fifth. Next common was drowsiness followed by loss of appetite. Generally the trend was to slightly lower reporting rates with sequential doses. Low grade fever was very common. Fever >39^{0}C was common, although <1% had fever >40^{0}C. The pattern did not indicate that higher rates of general symptoms occurred with MenACWY-TT compared to the two monovalent MenC groups.

		ACWY_3					ACWY_2					MenCCRM					MenC-TT				
					95 % CI					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Overall/dose																					
Drowsiness	All	1534	711	46.3	43.8	48.9	1554	686	44.1	41.7	46.7	1522	713	46.8	44.3	49.4	1536	701	45.6	43.1	48.2
	Grade 3	1534	63	4.1	3.2	5.2	1554	49	3.2	2.3	4.1	1522	47	3.1	2.3	4.1	1536	60	3.9	3.0	5.0
	Related	1534	408	26.6	24.4	28.9	1554	405	26.1	23.9	28.3	1522	409	26.9	24.7	29.2	1536	422	27.5	25.3	29.8
	Grade 3 Related	1534	53	3.5	2.6	4.5	1554	30	1.9	1.3	2.7	1522	24	1.6	1.0	2.3	1536	48	3.1	2.3	4.1
	Medical advice	1534	3	0.2	0.0	0.6	1554	2	0.1	0.0	0.5	1522	4	0.3	0.1	0.7	1536	1	0.1	0.0	0.4
Irritability	All	1534	916	59.7	57.2	62.2	1554	928	59.7	57.2	62.2	1522	945	62.1	59.6	64.5	1536	946	61.6	59.1	64.0
	Grade 3	1534	143	9.3	7.9	10.9	1554	106	6.8	5.6	8.2	1522	121	8.0	6.6	9.4	1536	141	9.2	7.8	10.7
	Related	1534	572	37.3	34.9	39.8	1554	582	37.5	35.0	39.9	1522	571	37.5	35.1	40.0	1536	621	40.4	38.0	42.9
	Grade 3 Related	1534	121	7.9	6.6	9.4	1554	88	5.7	4.6	6.9	1522	81	5.3	4.2	6.6	1536	113	7.4	6.1	8.8
	Medical advice	1534	6	0.4	0.1	0.8	1554	8	0.5	0.2	1.0	1522	7	0.5	0.2	0.9	1536	5	0.3	0.1	0.8
Loss of appetite	All	1534	501	32.7	30.3	35.1	1554	569	36.6	34.2	39.1	1522	538	35.3	32.9	37.8	1536	552	35.9	33.5	38.4
	Grade 3	1534	36	2.3	1.6	3.2	1554	28	1.8	1.2	2.6	1522	25	1.6	1.1	2.4	1536	24	1.6	1.0	2.3
	Related	1534	278	18.1	16.2	20.1	1554	303	19.5	17.6	21.6	1522	287	18.9	16.9	20.9	1536	313	20.4	18.4	22.5
	Grade 3 Related	1534	29	1.9	1.3	2.7	1554	16	1.0	0.6	1.7	1522	12	0.8	0.4	1.4	1536	16	1.0	0.6	1.7
	Medical advice	1534	2	0.1	0.0	0.5	1554	8	0.5	0.2	1.0	1522	6	0.4	0.1	0.9	1536	3	0.2	0.0	0.6
Temperature/(Rectally) (°C)	All	1534	418	27.2	25.0	29.6	1554	434	27.9	25.7	30.2	1522	440	28.9	26.6	31.3	1536	441	28.7	26.5	31.0
	≥38	1534	418	27.2	25.0	29.6	1554	434	27.9	25.7	30.2	1522	440	28.9	26.6	31.3	1536	441	28.7	26.5	31.0
	>38.5	1534	117	7.6	6.3	9.1	1554	125	8.0	6.7	9.5	1522	129	8.5	7.1	10.0	1536	143	9.3	7.9	10.9
	>39.0	1534	22	1.4	0.9	2.2	1554	35	2.3	1.6	3.1	1522	41	2.7	1.9	3.6	1536	31	2.0	1.4	2.9
	>39.5	1534	5	0.3	0.1	0.8	1554	7	0.5	0.2	0.9	1522	14	0.9	0.5	1.5	1536	5	0.3	0.1	0.8
	>40.0	1534	1	0.1	0.0	0.4	1554	2	0.1	0.0	0.5	1522	3	0.2	0.0	0.6	1536	2	0.1	0.0	0.5
	Related	1534	306	19.9	18.0	22.0	1554	312	20.1	18.1	22.2	1522	317	20.8	18.8	23.0	1536	343	22.3	20.3	24.5
	>40.0 Related	1534	1	0.1	0.0	0.4	1554	0	0.0	0.0	0.2	1522	2	0.1	0.0	0.5	1536	2	0.1	0.0	0.5
	Medical advice	1534	19	1.2	0.7	1.9	1554	13	0.8	0.4	1.4	1522	16	1.1	0.6	1.7	1536	10	0.7	0.3	1.2
Overall/subject																					
Drowsiness	All	518	376	72.6	68.5	76.4	523	365	69.8	65.7	73.7	509	370	72.7	68.6	76.5	518	377	72.8	68.7	76.6
	Grade 3	518	45	8.7	6.4	11.5	523	41	7.8	5.7	10.5	509	40	7.9	5.7	10.5	518	47	9.1	6.7	11.9
	Related	518	235	45.4	41.0	49.8	523	231	44.2	39.9	48.5	509	235	46.2	41.8	50.6	518	237	45.8	41.4	50.2
	Grade 3 Related	518	38	7.3	5.2	9.9	523	25	4.8	3.1	7.0	509	22	4.3	2.7	6.5	518	40	7.7	5.6	10.4
	Medical advice	518	3	0.6	0.1	1.7	523	2	0.4	0.0	1.4	509	4	0.8	0.2	2.0	518	1	0.2	0.0	1.1
Irritability	All	518	419	80.9	77.2	84.2	523	436	83.4	79.9	86.5	509	439	86.2	82.9	89.1	518	441	85.1	81.8	88.1
	Grade 3	518	109	21.0	17.6	24.8	523	83	15.9	12.8	19.3	509	86	16.9	13.7	20.4	518	104	20.1	16.7	23.8
	Related	518	302	58.3	53.9	62.6	523	304	58.1	53.8	62.4	509	311	61.1	56.7	65.4	518	325	62.7	58.4	66.9
	Grade 3 Related	518	93	18.0	14.7	21.5	523	69	13.2	10.4	16.4	509	65	12.8	10.0	16.0	518	87	16.8	13.7	20.3
	Medical advice	518	6	1.2	0.4	2.5	523	8	1.5	0.7	3.0	509	7	1.4	0.6	2.8	518	5	1.0	0.3	2.2
Loss of appetite	All	518	295	56.9	52.6	61.3	523	325	62.1	57.8	66.3	509	307	60.3	55.9	64.6	518	312	60.2	55.9	64.5
	Grade 3	518	28	5.4	3.6	7.7	523	23	4.4	2.8	6.5	509	22	4.3	2.7	6.5	518	22	4.2	2.7	6.4
	Related	518	180	34.7	30.6	39.0	523	194	37.1	32.9	41.4	509	186	36.5	32.3	40.9	518	182	35.1	31.0	39.4
	Grade 3 Related	518	24	4.6	3.0	6.8	523	15	2.9	1.6	4.7	509	11	2.2	1.1	3.8	518	15	2.9	1.6	4.7
	Medical advice	518	2	0.4	0.0	1.4	523	8	1.5	0.7	3.0	509	6	1.2	0.4	2.5	518	3	0.6	0.1	1.7
Temperature/(Rectally) (°C)	All	518	272	52.5	48.1	56.9	523	274	52.4	48.0	56.7	509	277	54.4	50.0	58.8	518	275	53.1	48.7	57.5
	≥38	518	272	52.5	48.1	56.9	523	274	52.4	48.0	56.7	509	277	54.4	50.0	58.8	518	275	53.1	48.7	57.5
	>38.5	518	98	18.9	15.6	22.6	523	101	19.3	16.0	23.0	509	101	19.8	16.5	23.6	518	116	22.4	18.9	26.2
	>39.0	518	20	3.9	2.4	5.9	523	30	5.7	3.9	8.1	509	34	6.7	4.7	9.2	518	28	5.4	3.6	7.7
	>39.5	518	5	1.0	0.3	2.2	523	7	1.3	0.5	2.7	509	13	2.6	1.4	4.3	518	5	1.0	0.3	2.2
	>40.0	518	1	0.2	0.0	1.1	523	2	0.4	0.0	1.4	509	3	0.6	0.1	1.7	518	2	0.4	0.0	1.4
	Related	518	203	39.2	35.0	43.5	523	208	39.8	35.5	44.1	509	208	40.9	36.6	45.3	518	220	42.5	38.2	46.9
	>40.0 Related	518	1	0.2	0.0	1.1	523	0	0.0	0.0	0.7	509	2	0.4	0.0	1.4	518	2	0.4	0.0	1.4
	Medical advice	518	19	3.7	2.2	5.7	523	13	2.5	1.3	4.2	509	15	2.9	1.7	4.8	518	10	1.9	0.9	3.5

Tabulations are also provided by country but there are too few subjects from Estonia to comment. For Germany and Spain the reporting rates for solicited symptoms overall by subject were broadly similar between countries.

At least one unsolicited AE was reported by 52-57% of subjects in each treatment group. Grade 3 unsolicited AEs were reported in ~3-5% per group, most commonly bronchiolitis, bronchitis, URTI and gastroenteritis. Most occurred within the first 4 days of a dose. Overall, the unsolicited AEs were very scattered in nature by PT. Skin rashes, collectively, were very common but individual rash types were diverse.

Drug-related AEs were reported for ~2-4% per group, most commonly diarrhoea, vomiting and injection site induration. As shown below, these were also scattered in nature. Apart from the AEs associated with the injection site it seems unlikely that the others were related to vaccination. The unsolicited AEs of epilepsy and hypotonia were both Grade 3 and serious. The case of hypotonia was in the MenC-CRM197 group. The case of epilepsy occurred in the 3-dose MenACWY-TT group and is discussed below.

Table 18. Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term with causal relationship to vaccination, within the 31-day (Days 0-30) post-vaccination period (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		20	3.8	2.3	5.8	12	2.3	1.2	4.0	17	3.3	1.9	5.2	15	2.8	1.6	4.7
Gastrointestinal disorders (10017947)	Abdominal pain (10000081)	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
	Constipation (10010774)	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
	Diarrhoea (10012735)	4	0.8	0.2	1.9	4	0.8	0.2	1.9	1	0.2	0.0	1.1	3	0.6	0.1	1.7
	Flatulence (10016766)	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)	4	0.8	0.2	1.9	1	0.2	0.0	1.1	3	0.6	0.1	1.7	1	0.2	0.0	1.1
General disorders and administration site conditions (10018065)	Crying (10011469)	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
	Discomfort (10013082)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1	1	0.2	0.0	1.1
	Inflammation (10061218)	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
	Injection site bruising (10022052)	1	0.2	0.0	1.1	1	0.2	0.0	1.1	1	0.2	0.0	1.1	0	0.0	0.0	0.7
	Injection site discolouration (10051572)	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
	Injection site erythema (10022061)	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
	Injection site haematoma (10022066)	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
	Injection site induration (10022075)	1	0.2	0.0	1.1	2	0.4	0.0	1.4	1	0.2	0.0	1.1	4	0.8	0.2	1.9
	Injection site nodule (10057880)	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
	Injection site reaction (10022095)	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
	Peripheral swelling (10048959)	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
	Pyrexia (10037660)	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
Infections and infestations (10021881)	Candida infection (10074170)	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
	Conjunctivitis (10010741)	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 (10017888)	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
	Nasopharyngitis (10028810)	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
	Upper respiratory tract infection (10046306)	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
Musculoskeletal and connective tissue disorders (10028395)	Muscular weakness (10028372)	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	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

		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**
Psychiatric disorders (10037175)	Insomnia (10022437)	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
	Irritability (10022998)	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
	Restlessness (10038743)	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
	Sleep disorder (10040984)	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
Respiratory, thoracic and mediastinal disorders (10038738)	Dysphonia (10013952)	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
	Hiccups (10020039)	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
Skin and subcutaneous tissue disorders (10040785)	Eczema (10014184)	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
	Rash (10037844)	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
	Seborrhoeic dermatitis (10039793)	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

(from table 379 – Module 5.3.5.1 study report body)

AEs in the booster phase to ESFU (6 months post-booster dose)

All subjects vaccinated in the booster phase received a dose of meningococcal vaccine and all except one in the MenC-CRM197 group (99.8%) received the designated additional vaccines. During the 8-day follow-up period, at least one symptom (solicited or unsolicited) was reported in 86-89% per group and most were considered to be vaccine-related. Grade 3 symptoms were reported in ~22% per group. The majority was reported during the 4-day follow-up period.

Table 19. Incidence and nature of symptoms (solicited and unsolicited) 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	442	88.9	85.8	91.6	497	386	77.7	73.7	81.3	497	355	71.4	67.2	75.4
ACWY_2	511	439	85.9	82.6	88.8	511	385	75.3	71.4	79.0	511	372	72.8	68.7	76.6
MenCCRM	503	444	88.3	85.1	90.9	503	377	75.0	70.9	78.7	503	369	73.4	69.3	77.2
MenC-TT	506	445	87.9	84.8	90.7	506	386	76.3	72.3	79.9	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

(from table 408 – Module 5.3.5.1 study report body)

Redness and pain were the most frequently reported solicited local symptoms in all four groups. Grade 3 redness was reported in 0.6-1.2% per group but Grade 3 pain was reported in ~4-6%. When viewed by vaccine injection site local symptoms were generally less common at the meningococcal vaccine sites compared to Infanrix hexa or Synflorix sites.

Table 20. Incidence of solicited local symptoms reported during the 8-days (Days 0-7) post-booster vaccination period (Booster Total Vaccinated cohort)

		ACWY_3					ACWY_2					MenCCRM					MenC-TT				
					95 % CI					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Pain	All	491	268	54.6	50.1	59.0	510	266	52.2	47.7	56.6	496	272	54.8	50.3	59.3	504	252	50.0	45.5	54.5
	Grade 3	491	44	9.0	6.6	11.8	510	41	8.0	5.8	10.7	496	48	9.7	7.2	12.6	504	35	6.9	4.9	9.5
	Medical advice	491	1	0.2	0.0	1.1	510	1	0.2	0.0	1.1	496	0	0.0	0.0	0.7	504	0	0.0	0.0	0.7
Redness (mm)	All	491	287	58.5	54.0	62.9	510	314	61.6	57.2	65.8	496	311	62.7	58.3	67.0	504	312	61.9	57.5	66.2
	>30	491	38	7.7	5.5	10.5	510	33	6.5	4.5	9.0	496	46	9.3	6.9	12.2	504	31	6.2	4.2	8.6
	Medical advice	491	1	0.2	0.0	1.1	510	0	0.0	0.0	0.7	496	3	0.6	0.1	1.8	504	0	0.0	0.0	0.7
Swelling (mm)	All	491	249	50.7	46.2	55.2	510	260	51.0	46.5	55.4	496	268	54.0	49.5	58.5	504	273	54.2	49.7	58.6
	>30	491	22	4.5	2.8	6.7	510	22	4.3	2.7	6.5	496	19	3.8	2.3	5.9	504	22	4.4	2.8	6.5
	Medical advice	491	0	0.0	0.0	0.7	510	1	0.2	0.0	1.1	496	1	0.2	0.0	1.1	504	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 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 documented dose
n/%= number/percentage of subjects reporting the symptom at least once
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

(from table 415 – Module 5.3.5.1 study report body)

Irritability was the most frequently reported solicited general symptom (~58% in each group) with Grade 3 irritability in 7-9% per group. About one third had fever after the booster dose. Fever >39^{0}C was common.

Table 21. Incidence of solicited general symptoms reported during the 8-day (Days 0-7) post-booster vaccination period (Booster Total Vaccinated cohort)

		ACWY_3					ACWY_2					MenCCRM					MenC-TT				
					95 % CI					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Drowsiness	All	491	198	40.3	36.0	44.8	510	206	40.4	36.1	44.8	496	208	41.9	37.6	46.4	504	202	40.1	35.8	44.5
	Grade 3	491	14	2.9	1.6	4.7	510	13	2.5	1.4	4.3	496	21	4.2	2.6	6.4	504	18	3.6	2.1	5.6
	Related	491	125	25.5	21.7	29.6	510	129	25.3	21.6	29.3	496	119	24.0	20.3	28.0	504	125	24.8	21.1	28.8
	Grade 3 Related	491	9	1.8	0.8	3.5	510	9	1.8	0.8	3.3	496	14	2.8	1.6	4.7	504	11	2.2	1.1	3.9
	Medical advice	491	1	0.2	0.0	1.1	510	0	0.0	0.0	0.7	496	2	0.4	0.0	1.4	504	3	0.6	0.1	1.7
Irritability	All	491	284	57.8	53.3	62.3	510	296	58.0	53.6	62.4	496	284	57.3	52.8	61.7	504	297	58.9	54.5	63.3
	Grade 3	491	41	8.4	6.1	11.2	510	37	7.3	5.2	9.9	496	37	7.5	5.3	10.1	504	45	8.9	6.6	11.8
	Related	491	180	36.7	32.4	41.1	510	197	38.6	34.4	43.0	496	181	36.5	32.2	40.9	504	186	36.9	32.7	41.3
	Grade 3 Related	491	32	6.5	4.5	9.1	510	32	6.3	4.3	8.7	496	26	5.2	3.5	7.6	504	31	6.2	4.2	8.6
	Medical advice	491	2	0.4	0.0	1.5	510	1	0.2	0.0	1.1	496	4	0.8	0.2	2.1	504	3	0.6	0.1	1.7
Loss of appetite	All	491	189	38.5	34.2	43.0	510	193	37.8	33.6	42.2	496	198	39.9	35.6	44.4	504	195	38.7	34.4	43.1
	Grade 3	491	12	2.4	1.3	4.2	510	21	4.1	2.6	6.2	496	23	4.6	3.0	6.9	504	27	5.4	3.6	7.7
	Related	491	118	24.0	20.3	28.1	510	114	22.4	18.8	26.2	496	114	23.0	19.4	26.9	504	121	24.0	20.3	28.0
	Grade 3 Related	491	7	1.4	0.6	2.9	510	15	2.9	1.7	4.8	496	13	2.6	1.4	4.4	504	18	3.6	2.1	5.6
	Medical advice	491	1	0.2	0.0	1.1	510	0	0.0	0.0	0.7	496	4	0.8	0.2	2.1	504	4	0.8	0.2	2.0
Temperature/(Rectally) (°C)	All	491	187	38.1	33.8	42.5	510	180	35.3	31.1	39.6	496	186	37.5	33.2	41.9	504	170	33.7	29.6	38.0
	≥38	491	187	38.1	33.8	42.5	510	180	35.3	31.1	39.6	496	186	37.5	33.2	41.9	504	170	33.7	29.6	38.0
	>38.5	491	84	17.1	13.9	20.7	510	84	16.5	13.4	20.0	496	80	16.1	13.0	19.7	504	67	13.3	10.5	16.6
	>39.0	491	31	6.3	4.3	8.8	510	33	6.5	4.5	9.0	496	43	8.7	6.3	11.5	504	26	5.2	3.4	7.5
	>39.5	491	12	2.4	1.3	4.2	510	12	2.4	1.2	4.1	496	18	3.6	2.2	5.7	504	9	1.8	0.8	3.4
	>40.0	491	2	0.4	0.0	1.5	510	2	0.4	0.0	1.4	496	3	0.6	0.1	1.8	504	7	1.4	0.6	2.8
	Related	491	133	27.1	23.2	31.3	510	132	25.9	22.1	29.9	496	122	24.6	20.9	28.6	504	125	24.8	21.1	28.8
	>40.0 Related	491	2	0.4	0.0	1.5	510	0	0.0	0.0	0.7	496	2	0.4	0.0	1.4	504	3	0.6	0.1	1.7
	Medical advice	491	14	2.9	1.6	4.7	510	10	2.0	0.9	3.6	496	14	2.8	1.6	4.7	504	11	2.2	1.1	3.9

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 documented dose
n/%= number/percentage of subjects reporting the symptom at least once
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

(from table 420 – Module 5.3.5.1 study report body)

At least one unsolicited AE was reported by about one third of subjects per group and Grade 3 events were reported in ~3, most frequently gastroenteritis and URTI. About 1% of subjects had unsolicited AEs considered by the investigator to be causally related but these were scattered in nature, as shown below.

Table 22. Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term with causal relationship to vaccination, within the 31-day (Days 0-30) post-vaccination period (Booster Total Vaccinated cohort)

		ACWY_3 N = 497				ACWY_2 N = 511				MenCCRM N = 503				MenC-TT N = 506			
				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		4	0.8	0.2	2.0	5	1.0	0.3	2.3	5	1.0	0.3	2.3	4	0.8	0.2	2.0
Gastrointestinal disorders (10017947)	Constipation (10010774)	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
	Diarrhoea (10012735)	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
	Vomiting (10047700)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	2	0.4	0.0	1.4	0	0.0	0.0	0.7
General disorders and administration site conditions (10018065)	Application site pruritus (10003053)	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
	Asthenia (10003549)	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
	Injection site haematoma (10022066)	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
	Injection site induration (10022075)	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
Infections and infestations (10021881)	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
	Upper respiratory tract infection (10046306)	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
Nervous system disorders (10029205)	Balance disorder (10049848)	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
Psychiatric disorders (10037175)	Sleep disorder (10040984)	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)	Rash (10037844)	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 = 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
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the 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

(from table 424 – Module 5.3.5.1 study report body)

Serious adverse event / deaths / other significant events

Deaths and SAEs

There were no fatal events reported at any stage of the study.

Any SAE was reported up to the day preceding the booster dose by ~6-8% per group but none was considered vaccine-related. Any SAE was reported from the primary vaccination to the end of the ESFU (6 months after the booster dose) by ~10% per group. In both cases bronchiolitis and bronchitis predominated.

From study start to one month post-primary vaccination, one subject had an SAE of epilepsy which was considered by the investigator to be vaccine related. The onset occurred 7 days after the third dose of MenACWY-TT, the subject was hospitalised and was recorded as still recovering at the cut-off date (05 November 2015). One subject in the MenC-TT group reported four SAEs considered not related to study vaccines (bronchitis, elevated AST, ALT and ALP). The subject was hospitalized for 3 days after the onset of bronchitis which occurred 37 days after vaccination with Synflorix and Infanrix hexa (dose 2) and this resolved. The elevated enzymes occurred 38 and 97 days after vaccination and did not recover/resolve. One SAE of febrile convulsion was reported up to the pre-boost visit. This occurred in the 3-dose MenACWY group but the onset was several months after the third dose.

Any SAE was reported from the booster vaccination up to the end of the ESFU by ~3% per group but none was considered vaccine-related. There were 3 additional SAEs of febrile convulsion but these cases occurred in the monovalent meningococcal conjugate groups.

Table 23. Percentage of subjects reporting Serious Adverse Events classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-booster vaccination period (Booster Total Vaccinated cohort)

		ACWY_3 N = 497				ACWY_2 N = 511				MenCCRM N = 503				MenC-TT N = 506			
				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		1	0.2	0.0	1.1	5	1.0	0.3	2.3	3	0.6	0.1	1.7	4	0.8	0.2	2.0
Gastrointestinal disorders (10017947)	Vomiting (10047700)	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
General disorders and administration site conditions (10018065)	Pyrexia (10037660)	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
Infections and infestations (10021881)	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
	Bronchitis (10006451)	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
	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
	Gastroenteritis (10017888)	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
	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
	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
	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
	Upper respiratory tract infection (10046306)	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)	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
Reproductive system and breast disorders (10038604)	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)	Bronchial hyperreactivity (10066091)	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
	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

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
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the 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

(from table 426 – Module 5.3.5.1 study report body)

Other significant AEs

AEs of specific interest (New Onset Chronic Illness; NOCIs) were reported up to the day preceding the booster dose by ~2% per treatment group.

Table 24. Percentage of subjects reporting new onset of chronic illness (NOCI) 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		12	2.3	1.2	3.9	10	1.9	0.9	3.5	10	1.9	0.9	3.5	8	1.5	0.7	3.0
Immune system disorders (10021428)	Food allergy (10016946)	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
	Hypersensitivity (10020751)	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
	Milk allergy (10027633)	1	0.2	0.0	1.1	3	0.6	0.1	1.7	2	0.4	0.0	1.4	1	0.2	0.0	1.1
Investigations (10022891)	Cold agglutinins positive (10009854)	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	0	0.0	0.0	0.7	0	0.0	0.0	0.7
Respiratory, thoracic and mediastinal disorders (10038738)	Bronchial hyperreactivity (10066091)	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
	Bronchospasm (10006482)	5	0.9	0.3	2.2	2	0.4	0.0	1.4	1	0.2	0.0	1.1	1	0.2	0.0	1.1
Skin and subcutaneous tissue disorders (10040785)	Dermatitis atopic (10012438)	4	0.8	0.2	1.9	4	0.8	0.2	1.9	3	0.6	0.1	1.7	3	0.6	0.1	1.7
	Dermatitis contact (10012442)	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
	Urticaria (10046735)	1	0.2	0.0	1.1	0	0.0	0.0	0.7	2	0.4	0.0	1.4	0	0.0	0.0	0.7

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

(from table 383 – Module 5.3.5.1 study report body)

AEs of specific interest were reported post-booster vaccination up to the end of the ESFU in ≤1.0% of subjects per group.

Table 25. Percentage of subjects reporting New Onset of Chronic Illness classified by MedDRA Primary System Organ Class and Preferred Term from booster vaccination up to end of ESFU (Booster Total Vaccinated cohort)

		ACWY_3 N = 497				ACWY_2 N = 511				MenCCRM N = 503				MenC-TT N = 506			
				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		2	0.4	0.0	1.4	2	0.4	0.0	1.4	5	1.0	0.3	2.3	3	0.6	0.1	1.7
Gastrointestinal disorders (10017947)	Coeliac disease (10009839)	0	0.0	0.0	0.7	0	0.0	0.0	0.7	1	0.2	0.0	1.1	1	0.2	0.0	1.1
Immune system disorders (10021428)	Food allergy (10016946)	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)	Asthma (10003553)	0	0.0	0.0	0.7	1	0.2	0.0	1.1	1	0.2	0.0	1.1	2	0.4	0.0	1.4
	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)	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
Skin and subcutaneous tissue disorders (10040785)	Dermatitis atopic (10012438)	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

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 ag
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
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the 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

(from table 428 – Module 5.3.5.1 study report body)

Laboratory findings

Abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g. electrocardiograms, X-rays, vital signs) that were judged by the investigator to be clinically significant were to be recorded as AEs or SAEs if they met the definition of an AE or SAE. Clinically significant abnormal laboratory findings or other abnormal assessments that were detected

during the study or were present at baseline and significantly worsened following the start of the study were to be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that were associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that were present or detected at the start of the study and did not worsen, were not to be reported as AEs or SAEs.

Safety related to drug-drug interactions and other interactions

Concomitant medications /vaccinations

In the primary phase intake of concomitant medication(s) was reported for about half the subjects in each group during the 8-day post-vaccination period. Although ~35% per group received antipyretic medication < 2% received a prophylactic antipyretic. Most of the intake was during the 4-day post-vaccination period. During 31 days post-dose use of concomitant medication(s) was reported for ~60% per group and ~40% received antipyretic medication.

Table 26. Percentage of subjects with concomitant medication during the 8- days (Days 0-7) post-vaccination period by dose and overall (Primary Total Vaccinated cohort)

	ACWY_3					ACWY_2					MenCCRM					MenC-TT				
				95% CI					95% CI					95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1																				
Any	528	177	33.5	29.5	37.7	524	159	30.3	26.4	34.5	516	162	31.4	27.4	35.6	527	160	30.4	26.5	34.5
Any antipyretic	528	134	25.4	21.7	29.3	524	120	22.9	19.4	26.7	516	118	22.9	19.3	26.7	527	122	23.1	19.6	27.0
Prophylactic antipyretic	528	5	0.9	0.3	2.2	524	7	1.3	0.5	2.7	516	4	0.8	0.2	2.0	527	4	0.8	0.2	1.9
Dose 2																				
Any	513	159	31.0	27.0	35.2	520	145	27.9	24.1	32.0	509	158	31.0	27.0	35.3	515	138	26.8	23.0	30.8
Any antipyretic	513	100	19.5	16.2	23.2	520	97	18.7	15.4	22.3	509	106	20.8	17.4	24.6	515	83	16.1	13.0	19.6
Prophylactic antipyretic	513	7	1.4	0.6	2.8	520	3	0.6	0.1	1.7	509	5	1.0	0.3	2.3	515	6	1.2	0.4	2.5
Dose 3																				
Any	511	141	27.6	23.8	31.7	518	149	28.8	24.9	32.9	509	126	24.8	21.1	28.7	511	133	26.0	22.3	30.1
Any antipyretic	511	74	14.5	11.5	17.8	518	82	15.8	12.8	19.3	509	73	14.3	11.4	17.7	511	82	16.0	13.0	19.5
Prophylactic antipyretic	511	3	0.6	0.1	1.7	518	2	0.4	0.0	1.4	509	2	0.4	0.0	1.4	511	5	1.0	0.3	2.3
Overall/dose																				
Any	1552	477	30.7	28.4	33.1	1562	453	29.0	26.8	31.3	1534	446	29.1	26.8	31.4	1553	431	27.8	25.5	30.1
Any antipyretic	1552	308	19.8	17.9	21.9	1562	299	19.1	17.2	21.2	1534	297	19.4	17.4	21.4	1553	287	18.5	16.6	20.5
Prophylactic antipyretic	1552	15	1.0	0.5	1.6	1562	12	0.8	0.4	1.3	1534	11	0.7	0.4	1.3	1553	15	1.0	0.5	1.6
Overall/subject																				
Any	528	277	52.5	48.1	56.8	524	274	52.3	47.9	56.6	516	256	49.6	45.2	54.0	527	260	49.3	45.0	53.7
Any antipyretic	528	184	34.8	30.8	39.1	524	187	35.7	31.6	40.0	516	178	34.5	30.4	38.8	527	182	34.5	30.5	38.8
Prophylactic antipyretic	528	10	1.9	0.9	3.5	524	10	1.9	0.9	3.5	516	7	1.4	0.5	2.8	527	10	1.9	0.9	3.5

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 who took the specified concomitant medication at least once during the mentioned period
For overall/dose:
N = number of administered doses
n/% = number/percentage of doses after which the specified concomitant medication was taken by subjects at least once during the mentioned period
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

(from table 386 – Module 5.3.5.1 study report body)

After the booster dose intake of concomitant medication(s) was reported for about one third of subjects in each treatment group. About 20% received any antipyretic but < 1% received a prophylactic antipyretic. Most use was within 4 days of the dose. Up to 31 days post-booster about 40% had concomitant medication(s) and about 25% received any antipyretic.

Table 27. Percentage of subjects with concomitant medication during the 8- days (Days 0-7) post-booster vaccination period (Booster Total Vaccinated cohort)

	ACWY_3					ACWY_2					MenCCRM					MenC-TT				
				95% CI					95% CI					95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Any	497	153	30.8	26.8	35.0	511	165	32.3	28.3	36.5	503	168	33.4	29.3	37.7	506	156	30.8	26.8	35.1
Any antipyretic	497	103	20.7	17.2	24.6	511	121	23.7	20.1	27.6	503	109	21.7	18.1	25.5	506	93	18.4	15.1	22.0
Prophylactic antipyretic	497	1	0.2	0.0	1.1	511	0	0.0	0.0	0.7	503	3	0.6	0.1	1.7	506	3	0.6	0.1	1.7

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 who took the specified concomitant medication at least once during the mentioned period
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

(from table 430 – Module 5.3.5.1 study report body)

Discontinuation due to adverse events

Five subjects withdrew due to an AE or SAE during the primary phase of the study. Two withdrew due to SAEs and one withdrew due to an AE in the ACWY_3 group. One subject withdrew due to an SAE in the MenC-CRM197 group and one withdrew due to an AE in the MenC-TT group. The three SAEs in two subjects leading to withdrawal from the study were considered unrelated to study vaccine and were:

1) Apparent life threatening illness/Epstein Barr Virus (EBV)
2) Muscle spasms
3) RSV bronchiolitis

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

Post marketing experience

Not applicable

2.5.1. Discussion on clinical safety

In light of co-administration of the meningococcal conjugate vaccines with Infanrix hexa and Synflorix in the primary and booster phases the overall safety profile was not substantially different between the four groups since it was driven by the background routine infant immunisations. The profile, including the range of unsolicited AEs, was typical of that observed with routine infant and toddler vaccinations and reflected what is already known about Infanrix hexa, Synflorix and the monovalent meningococcal conjugates. The rates of local and systemic symptoms did not increase with sequential doses and mostly decreased slightly.

Overall, the local reactogenicity of MenACWY-TT appeared to be similar to that of the monovalent MenC vaccines and these, collectively, were associated with fewer local symptoms than the background routine vaccines given, especially when compared with Infanrix hexa. The systemic symptom profiles were comparable across the four groups, reflecting the same background vaccines. The rate of fever was high and fevers exceeding 39^0C were common. In this study there was very little use of prophylactic anti-pyretic use. There does not seem to be a need to make a specific statement about prophylactic anti-pyretic use in the Nimenrix SmPC since this is covered by relevant SmPCs for co-administered

vaccines. Despite the lack of prophylactic anti-pyretics, there was a single febrile convulsion reported in a recipient of MenACWY-TT, which occurred a long time after the last dose and was not related.

With regard to the SAE of epilepsy which was considered by the investigator to be vaccine related and had onset 7 days after the third dose of MenACWY-TT, the MAH was asked to report the final outcome and provided an updated narrative. The investigators considered that the clinical picture of this boy could be due to an infectious disease or an intercurrent illness or could be related to vaccination. The investigator reports that the SAE of epilepsy resolved as of 20 October 2012. Whether or not vaccination was a trigger remains unsubstantiated. Even if this is the case, it is not possible to determine which vaccine might have been causative.

2.5.2. Conclusions on clinical safety

Study MenACWY-TT-083 showed that the overall safety profile was not substantially different between the four groups including the range of unsolicited AEs, and it was typical of that observed with routine infant and toddler vaccinations, reflecting what is already known about Infanrix hexa, Synflorix and the monovalent meningococcal conjugates. The rates of local and systemic symptoms did not increase with sequential doses and mostly decreased slightly.

Overall, the local reactogenicity of MenACWY-TT appeared to be similar to that of the monovalent MenC vaccines and both were associated with fewer local symptoms than the background routine vaccines given, especially when compared with Infanrix hexa. The systemic symptom profiles were comparable across the four groups, reflecting the same background vaccines. The rate of fever was high and fevers exceeding 39^0C were common, which was expected due to concomitant vaccinations and lack of use of anti-pyretics in the study.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR refers to the EURD list which remains unchanged.

2.6. Risk management plan

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

The PRAC considered that the risk management plan version 6.0 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 6.0 with the following content:

2.6.1. Safety concerns

Important identified risks	None
Important potential risks	Guillain-Barre Syndrome (GBS) Purpura Vasculitis Acute disseminated encephalomyelitis (ADEM) Brachial neuritis Anaphylaxis Change in meningococcal epidemiology/serogroup replacement Lack of efficacy Administration via the intravascular, intradermal or subcutaneous route Administration to patients with thrombocytopenia or any coagulation disorder with a risk of haemorrhage
Missing information	Use in immunocompromised and immunodeficient (including asplenic) patients; Use in patients with chronic diseases; Use during pregnancy and lactation; Long term persistence of the vaccine response and need for a booster dose.

2.6.2. Pharmacovigilance plan

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started	Date for Submission of Interim or Final Reports (Planned or Actual)
MenACWY-TT-043 (EXT:036 Y2/Y3/Y4/Y5) Phase III extension of study MenACWY-TT-036, open, controlled Category 3	To evaluate the long-term persistence of the immunogenicity induced by MenACWY-TT or Mencevax ACWY at 24, 36, 48, and 60 months after vaccination.	Safety and tolerability of the period of antibody persistence, and with regards to a booster dose.	Ongoing	December 2015
MenACWY-TT-059 (EXT:052 Y1/Y3/Y5) Phase II extension of study MenACWY-TT-052, open, controlled Category 3	To evaluate the long-term persistence of the immunogenicity induced by MenACWY-TT vaccine as compared to Menactra at 1, 3 and 5 years after vaccination.	Safety and tolerability of the period of antibody persistence, and with regards to a booster dose.	Ongoing	December 2015
MenACWY-TT-084 Phase III, open, controlled Category 3	To evaluate the immunogenicity of 1 and 2 doses of MenACWY-TT administered to at risk subjects (asplenic children or children having complement deficiencies) compared to age-matched healthy subjects in terms of rSBA and hSBA vaccine response rates for *N. meningitidis* serogroups A, C, W and Y.	Safety and tolerability of the period of antibody persistence, and with regards to a booster dose.	Ongoing	April 2016
MenACWY-TT-088 (EXT: 081 M32, M44, M56, M68) Phase III, open, randomized, controlled Category 3	To evaluate the long-term persistence of the immunogenicity induced by MenACWY-TT or *Menjugate* at 32, 44, 56 and 68 months after vaccination.	Safety and tolerability of the period of antibody persistence, and with regards to a booster dose.	Ongoing	December 2015
MenACWY-TT-099 (EXT:015Y6/Y7/Y8/Y9/Y10) Phase II extension of study MenACWY-TT-015, open, controlled Category 3	Persistence of the immunogenicity of MenACWY-TT compared to Mencevax ACWY 6 to 10 years after vaccination.	Safety and tolerability of the period of antibody persistence, and with regards to a booster dose.	Ongoing	April 2019

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started	Date for Submission of Interim or Final Reports (Planned or Actual)
MenACWY-TT-100 (EXT:027Y6/Y7/Y8/Y9/Y10) Phase IIb, extension of study MenACWY-TT-027, open, randomized, controlled Category 3	In subjects <2 years of age: To compare the persistence of the immunogenicity of MenACWY-TT conjugate vaccine with that of Meningitec 6 to 10 years after vaccination. In subjects ≥ 2 years of age: To compare the persistence of the immunogenicity of MenACWY-TT conjugate vaccine with that of Mencevax ACWY 6 to 10 years after vaccination.	Safety and tolerability of the period of antibody persistence, and with regards to a booster dose.	Ongoing	January 2019
MenACWY-TT-101 (EXT:036Y10) Phase III extension of study MenACWY-TT-036, open, controlled Category 3	To evaluate the immunogenicity, reactogenicity and safety of a booster dose of MenACWY-TT administered 10 years after healthy subjects aged 11-17 years received either MenACWY-TT or Mencevax ACWY™.	Safety and tolerability of the period of antibody persistence, and with regards to a booster dose.	Planned	December 2019
MenACWY-TT-102 (EXT :048Y6/Y7/Y8/Y9/Y10) Phase III extension of study MenACWY-TT-048, open, controlled Category 3	To evaluate the long-term antibody persistence at 2, 3, 4, 5 and 6 years after a booster dose of MenACWY-TT or Meningitec administered 4 years after priming at toddler age with the same vaccine.	Safety and tolerability of the period of antibody persistence with regards to a booster dose.	Ongoing	August 2019

2.6.3. Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important potential risks		
Guillain-Barre Syndrome (GBS)	None	None
Purpura	None	None
Vasculitis	None	None
Acute disseminated encephalomyelitis (ADEM)	None	None
Brachial neuritis	None	None
Anaphylaxis	Contraindication in section 4.3 (SmPC) for subject with "*hypersensitivity to the active substances or to any of the excipients*". Warning in section 4.4 (SmPC) explaining that "*Appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine*".	None
Change in meningococcal epidemiology/serogroup replacement	None	None
Lack of efficacy	Warning in section 4.4 (SmPC) explaining that "*A protective immune response may not be elicited in all vaccinees*".	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Administration via the intravascular, intradermal or subcutaneous route	In Posology and method of administration and method of administration section is explain the method of administration and in Special warnings and precautions for use explaining that "*Nimenrix should under no circumstances be administered intravascularly, intradermally or subcutaneously*".	None
Administration to patients with thrombocytopenia or any coagulation disorder with a risk of haemorrhage	Warning in section 4.4 (SmPC) explaining that "*Nimenrix should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following an intramuscular administration to these subjects*".	None
Missing Information		
Use in immunocompromised and immunodeficient (including asplenic) patients	None	None
Use in patients with chronic diseases	None	None
Use during pregnancy and lactation	None	None
Long term persistence of the vaccine response and need for a booster dose	None	None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly. The main SmPC changes are reflected below.

Section 4.1[1]:

Nimenrix is indicated for active immunisation of individuals from the age of ***6 weeks*** ~~*12 months and above*~~ *against invasive meningococcal diseases caused by Neisseria meningitidis group A, C, W-135, and Y.*

Section 4.2:

Posology

Nimenrix should be used in accordance with available official recommendations.

Infants from 6 to 12 weeks of age

The recommended immunisation series consists of three doses, each of 0.5 ml. The primary infant series consists of two doses, with the first dose given from 6 weeks of age and with an interval of 2 months between doses. The third (booster) dose is recommended at 12 months of age (see section 5.1).

In section 4.8 the MAH has added a short paragraph on infant data and has amended the table (AEs frequencies – see Product Information).

In addition to the new data included in section 5.1, during the procedure the CHMP recommended that section 5.1 be rationalised by age group. For example, all the data for infants, including booster responses, are shown in a single table for each of rSBA and hSBA (see Product Information).

[1] New text in bold, deleted text underlined.

Changes were also made to the PI to improve clarity, streamline redundant text and to incorporate changes of variations that concluded in parallel (variations II-45 and II-53). These changes were reviewed and accepted by the CHMP.

2.7.1. User consultation

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

- As part of the initial Marketing Authorisation Application for Nimenrix, the MAH performed a readability test of the Package Leaflet.
- An additional patient consultation for the proposed update has not been performed as it is considered that the changes in the Package Leaflet are not significant enough to warrant additional readability testing. Nimenrix was already intended for use in small children from 1 year of age on, with the extension of the indication to infants aged 2 months – 1 year, and from 1 dose in over 1's to 2 doses in infants the PL does change significantly. There is no change to the presentation, legal status, active substance or other changes as per the guideline which would warrant further consultation with the target patient group at this time.
- Further, the product will be administered by healthcare professionals who are trained to administer and follow dosing schedules for vaccines.

3. Benefit-Risk Balance

This variation does not impact in any way on the current approval for Nimenrix from the age of 12 months. Therefore the following sections consider only the new data and benefit-risk in infants when Nimenrix is used from 6 weeks of age.

Benefits

Beneficial effects

The MAH's study to identify a suitable regimen for use in infants was of adequate design and conduct. The inference of efficacy is based on a measure of functional antibody. There is adequate evidence available to support this approach and therefore an application based on comparisons of safety and SBA is acceptable. There is no appropriate comparator for MenA, W or Y in infants. Use of two MenCC vaccines with different conjugating proteins was appropriate.

The data support use of Nimenrix from 2 months of age. On request, the MAH provided a further breakdown of numbers aged 6-8 vs. >8 weeks at the time of the first dose (which showed similar proportions above and below 8 weeks) and their immune responses to meningococcal antigens to substantiate use from 6 weeks of age.

This study met all six of the pre-defined elements of the primary analysis, which was conducted in a hierarchical fashion using an appropriate non-inferiority margin. In the primary series the rSBA data indicated at least comparable responses to MenC between either 2 or 3 doses of MenACWY-TT and the two monovalent MenC conjugates. In addition, the data showed that the lower bounds of the 95% CI around the differences in percentages with MenC rSBA titres ≥1:8 were actually within -4%. On this basis, either of the two infant regimens of Nimenrix could be considered adequate for eliciting satisfactory immune responses to MenC. Only at the higher cut-offs, reflecting the differences in GMTs, was there a possible advantage for the monovalent MenC vaccines. Even then, >90% in the MenACWY groups had rSBA titres

≥1:128, hence it seems unlikely that the differences observed are clinically important. The post-primary hSBA titres also showed similar results.

Some of the findings suggested that 2 doses of MenACWY might actually be better than 3 doses. For example, rSBA GMTs for MenC were significantly lower for the 3-dose group compared to the other three groups (95% CI did not overlap). Overall, the 2-dose infant regimen of Nimenrix is considered acceptable with regard to immune responses to MenC. The rSBA responses to MenA, W and Y did not suggest an advantage for 3 vs. 2 doses of MenACWY-TT. In each case very high percentages in both groups had rSBA titres ≥1:8 at M3 of the study (i.e. at about 5 months of age). The lower confidence interval limits around the percentages with rSBA titres ≥1:8 were >80% for each meningococcal serogroup. This finding also applied to percentages with titres ≥1:128 except for MenY in the 3-dose group (76.6%) and MenA in the 2-dose group (78.2%). There is no comparator but the data support the adequacy of Nimenrix for use in infancy. Although descriptive, the hSBA data showed a very similar pattern of post-primary between-group comparisons as described for the rSBA data for each meningococcal serogroup. The hSBA data demonstrated a greater advantage for 2 vs. 3 doses of MenACWY-TT than the rSBA data.

Since there is no advantage for 3 vs. 2 doses of MenACWY-TT in infants, the 2-dose regimen, with at least 8 weeks between doses, is preferable.

Concerning interactions with other vaccines, the MAH conducted assays of immune responses to co-administered antigens for a representative sample from each treatment group, allowing assessing the impact of MenACWY-TT compared to MenC-CRM197 or MenC-TT. In addition, since all the data on immune responses to meningococcal antigens were obtained against the same background of co-administered vaccines, and since responses to MenACWY-TT were satisfactory in comparison to other treatment groups, it can be concluded that Nimenrix may be given with DTaP-IPV-HBV-PRP-T and with Synflorix. Such data cannot be used to support co-administration of MenACWY-TT with PRP-CRM197 or PRP-D constructs or with Prevenar13 in infancy.

Before and after the booster dose, the rSBA titres were generally comparable between the 2-dose and 3-dose MenACWY-TT groups. Exceptions were higher GMTs for MenW and MenY in the 2-dose vs. 3-dose group with non-overlapping 95% CI. Comparisons with the monovalent MenC groups showed similar proportions with pre- and post-boost titres ≥1:8 and ≥1:128 across the four groups with lower 95% CI within -4%. The post-boost GMTs for MenC rSBA were similar for the two MenACWY-TT and MenC-CRM197 groups but lower for all 3 vs. MenC-TT with 95% CI that did not overlap. This finding is in keeping with observations made in other studies with NeisVac-C. However, the MenC responses were highly satisfactory for all four groups. All four groups demonstrated an anamnestic response for MenC and the two Nimenrix groups demonstrated anamnestic responses for MenA, W and Y, supporting adequate priming with 2 or 3 doses in infancy. However, there was no strict control group (i.e. one dose of Nimenrix in subjects with no prior vaccination against meningococci) to confirm this supposition. The pre- and post-boost hSBA data showed a comparable pattern of post-boost responses vs. rSBA and further demonstrated anamnestic immune responses to the final dose of MenACWY-TT.

Experience has already demonstrated that a booster dose of MenC is needed. It is very reasonable to assume that this also applies to the other meningococcal serogroups. Immune responses at M12 are clearly anamnestic and can be expected to prolong protection. As in older age groups, for whom a single dose is currently recommended, the need for further doses later in life is not yet fully established. However, long term antibody persistence data for MenC suggest that there could be a benefit from an additional dose(s) after several years have elapsed. This may apply particularly to those who were at the younger end of the age range (e.g. < 5 years old) when first vaccinated. For the present, the SmPC should recommend a booster dose of Nimenrix at 12 months of age for those initially vaccinated in early infancy.

Uncertainty in the knowledge about the beneficial effects

As pointed out above, unlike MenC, there is no appropriate comparator for MenA, W or Y in EU infants. Therefore it is only possible to observe the titres obtained and interpret them in light of widely held assumptions regarding the predictive value of SBA for efficacy. The responses to MenA, W and Y were very high and the post-boost responses indicated anamnestic responses (although vaccination of an age-matched unvaccinated control group was not done). While the evidence does support use of Nimenrix in infants, with a mandatory booster at 12 months of age due to the anticipated waning of titres between M4 and M12 of age, the magnitude of the vaccine efficacy that will be conferred cannot be predicted.

For practical reasons immunogenicity was measured in pre-selected subsets. This is an acceptable strategy given the age range studied but it does mean that the available data do reflect subsets.

As with the monovalent MenCC vaccines and for use of Nimenrix in older age groups, it is not yet known whether further booster doses will be needed after the booster dose to be mandated at 12 months of age.

It is not yet known whether Nimenrix can be given with other possible concomitant vaccines, which poses limitations on the routine programmes into which it can fit without adding visits.

Risks

Unfavourable effects

After the primary series, redness was the most frequently reported solicited local symptom in all four groups (in ~70% of the subjects) during the 8-day post-vaccination period followed by pain and swelling. Irritability was the most frequently reported (in >80% of subjects) solicited general symptom in all four groups during the 8-day post-vaccination period. Next common was drowsiness followed by loss of appetite. Low grade fever was very common. Fever >39^{0}C was common, although <1% had fever >40^{0}C. In light of co-administration of the meningococcal conjugate vaccines with Infanrix hexa and Synflorix in the primary and booster phases the overall safety profile was not substantially different between the four groups studied, since it was driven by the background routine infant immunisations. The profile, including the range of unsolicited AEs, was typical of that observed with routine infant and toddler vaccinations and reflected what is already known about Infanrix hexa, Synflorix and the monovalent meningococcal conjugates. The rates of local and systemic symptoms did not increase with sequential doses and mostly decreased slightly.

Overall, the local reactogenicity of MenACWY-TT appeared to be similar to that of the monovalent MenC vaccines and these, collectively, were associated with fewer local symptoms than the background routine vaccines given, especially when compared with Infanrix hexa. The systemic symptom profiles were comparable across the four groups, reflecting the same background vaccines. The rate of fever was high and fevers exceeding 39^{0}C were common. In this study there was very little use of prophylactic anti-pyretic use. There does not seem to be a need to make a specific statement about prophylactic anti-pyretic use in the Nimenrix SmPC since this is covered by relevant SmPCs for co-administered vaccines. Despite the lack of prophylactic anti-pyretic agents there was a single febrile convulsion reported in a recipient of MenACWY-TT, which occurred a long time after the last dose and was not related.

Uncertainty in the knowledge about the unfavourable effects

There was no control group that received only Infanrix hexa and Synflorix for comparison. Nevertheless, the comparisons made suggest that the various meningococcal conjugates were not really contributing much to the overall safety profiles.

Just over 1000 subjects received at least one dose of Nimenrix in this study. Since the MAH proposes 2 rather than 3 doses the safety data from all subjects who received Nimenrix can be taken into account as

relevant. Whereas for a completely new vaccine this safety database for a vaccine potentially to be widely used in infants would be considered small, taking into account the wealth of safety information already available with Nimenrix itself in older age groups and with MenCC vaccines in infants as well as the actual data available there seems to be a sufficient database available.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Based on functional antibody responses, whether measured by rSBA or hSBA, two doses of Nimenrix in early infancy since 6 weeks of age with a booster dose at 12 months of age appears to elicit a high probability of protection in early life associated with efficient priming of the infant immune system, as demonstrated by the anamnestic responses to the booster dose at 12 months of age. For MenC the comparable responses observed with Nimenrix vs. licensed monovalent vaccines supports a conclusion on efficacy. Whereas the magnitude of protection against MenA, W and Y cannot be predicted from the SBA responses, all the available evidence supports a benefit. There is no indication at present that Nimenrix presents any additional safety concern over and above the routine infant vaccines with which it will be given.

Conclusion

Based on the above, the benefit-risk balance of Nimenrix is favourable for use in infants since 6 weeks of age in the approved indication.

4. Recommendations

Outcome

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

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include a wider paediatric population starting from 6 weeks of age for Nimenrix; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet and the RMP (version 6.0) are updated in accordance.

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

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include a wider paediatric population starting from 6 weeks of age for Nimenrix; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet and the RMP (version 6.0) are updated in accordance.

Summary

Please refer to the published Assessment Report Nimenrix H-2226-II-49-AR.