EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nimenrix

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

Procedure No. EMEA/H/C/002226/II/0016

Note

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

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1. Scientific discussion

1.1. Introduction

Quadrivalent meningococcal serogroups A, C, W- 135 and Y conjugate vaccine (Nimenrix, MenACWY-TT) consists of 5 μg of *Neisseria meningitidis* capsular polysaccharides A, C, W-135 and Y, each coupled to tetanus toxoid (TT) as carrier protein. The vaccine contains approximately 44 μg of TT per dose.

Nimenrix was first authorised in Europe on 20 April 2012 for the active immunisation of individuals from the age of 12 months and above against invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W-135 and Y.

A type II variation (EMEA/H/C/2226/II/009) to update the summary of product characteristics (SmPC) with antibody persistence data up to 4 years post primary immunisation with MenACWY-TT in different age cohorts is currently under review. The purpose of the present variation is to submit the final clinical study report (CSR) for the paediatric study MenACWY-TT-048 EXT: 039 Y5 in accordance with Article 46 of Regulation (EC) No 1901/2006. Additional post-booster persistence time points are planned to be evaluated in children who participated in study MenACWY-TT-048 EXT: 039 Y5. The MAH plans to update the SmPC once additional post-booster persistence data across different age groups and time points are available.

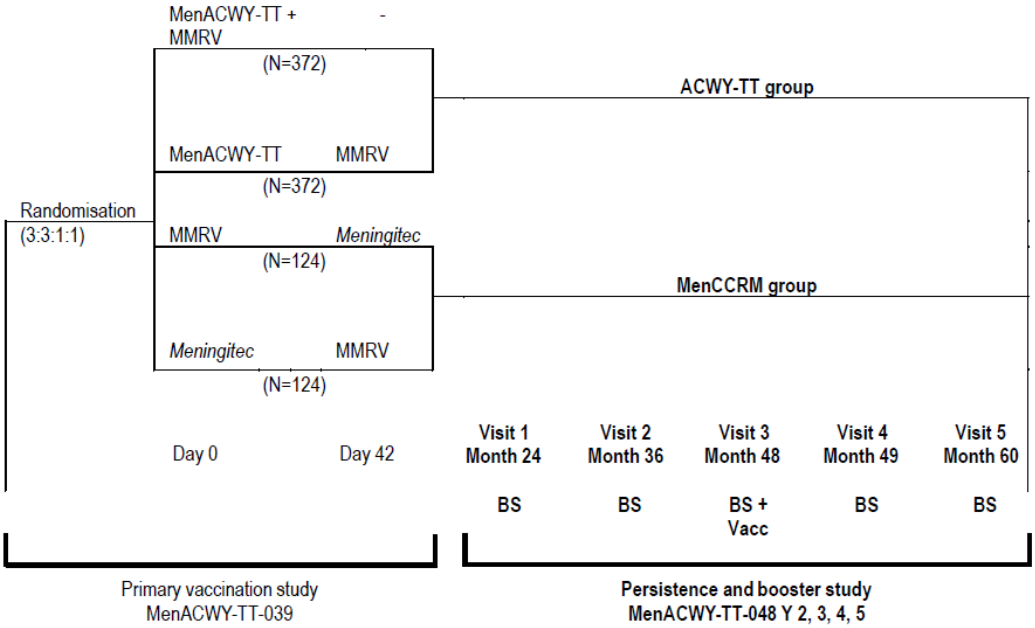
1.2. Clinical Efficacy aspects

The current CSR is the final report of study MenACWY-TT-048 EXT:039 Y2, 3, 4, 5 and provides antibody persistence assessment based on persistence at Month 60 i.e. up to 12 months after a booster dose, administered in children 60-69 months of age following priming with the same meningococcal vaccine at 12-23 months of age. The primary phase of study MenACWY-TT-039, as well as the annex CSR for the year 2 persistence time-point (MenACWY-TT-048 EXT: 039 Y2) were submitted as part of the initial marketing authorisation application for Nimenrix. Annex CSRs for the year 3 and 4 persistence time-points (MenACWY-TT-048 EXT: 039 Y3 and MenACWY-TT-048 EXT: 039 Y4), were submitted and assessed in accordance with Article 46 of Regulation (EC) No 1901/2006. The results of study MenACWY-TT-048 EXT: 039 Y4 are also included in the currently on-going type II variation (EMEA/H/C/2226/II/009).

1.2.1. Methods – analysis of data submitted

Study MenACWY-TT-048 EXT: 039 Y5 was a Phase III, randomised, open-label, controlled study with 2 parallel groups conducted at 14 different centres in Finland. The study design is illustrated in Figure 1.

Figure 1. Study design overview



BS = Blood sample
Vacc = Booster vaccination with the same meningococcal conjugate vaccine as given in the primary study MenACWY-TT-039.

Vaccination schedule

In the primary study MenACWY-TT-039, a total of 1000 children were enrolled and randomized (3:3:1:1) to receive vaccination with one dose of a meningococcal vaccine (MenACWY-TT, Nimenrix or MenC-CRM197, Meningitec) and two doses of combined measles, mumps, rubella and varicella vaccine (MMRV, Priorix Tetra) according to one of the following schedules:

- Co-ad group: Subjects received MenACWY-TT co-administered with Priorix- Tetra, followed by the second dose of Priorix-Tetra 84 days later;
- ACWY-TT group: Subjects received MenACWY-TT, followed by two doses of Priorix-Tetra, 42 and 84 days later;
- MMRV group: Subjects received Priorix-Tetra, followed by Meningitec 42 days later and the second dose of Priorix-Tetra 84 days later;
- MenCCRM group: Subjects received Meningitec, followed by two doses of Priorix-Tetra, 42 and 84 days later.

In study MenACWY-TT-048 EXT: 039, subjects primed with MenACWY-TT or Meningitec in the primary vaccination study were assigned to the ACWY-TT group and the MenCCRM group, respectively, and were boosted at four years after primary vaccination with the same meningococcal vaccine as given in the primary study. The study was conducted in an open manner as the primary vaccination study was conducted in an open manner and the presentation of the meningococcal vaccines was different.

Study population

Healthy male or female subjects who had been vaccinated in the primary vaccination phase and who did not receive any additional doses of meningococcal vaccine outside the MenACWY-TT-039 study were eligible to enrol for this year 5 persistence time point.

Methods used to evaluate immunogenicity

Immunological assessment comprised blood sampling for determination of antibodies to vaccine antigens. Blood samples were collected at each yearly persistence visit (Months 24, 36 and 48) and one and 12 months after the booster dose (Months 49 and 60). In this submission, only the results generated at Month 60, which were part of the secondary objectives of this study, are discussed. The evaluation of immunogenicity of meningococcal antibodies 12 months post booster dose with MenACWY-TT or Meningitec vaccine was performed in terms of:

- Serum Bactericidal Activity using rabbit complement (rSBA) antibody titres ≥ 1:8, ≥ 1:128, and geometric mean titres (GMTs) for each vaccine serogroup.
- Serum Bactericidal Activity using human complement (hSBA) antibody titres ≥ 1:4, ≥ 1:8, and GMTs for each vaccine serogroup.
- Anti-polysaccharide (anti-PS) antibody concentrations ≥ 0.3μg/mL, ≥ 2.0μg/mL, and geometric mean concentrations (GMCs) for each vaccine serogroup.

For samples collected in study MenACWY-TT-039 (prior to vaccination and on Day 42 post-primary vaccination) and in study MenACWY-TT-048 EXT: 039 Y2 (Month 24 post-primary vaccination), the rSBA and anti-PS testing was performed at the GSK laboratory. For samples collected in studies MenACWY-TT-048 EXT: 039 Y3, Y4 and Y5 (Months 36 and 48 post-primary vaccination, and Months 49 and 60 post-booster vaccination), the rSBA and anti-PS testing was performed at the laboratory of Public Health England (PHE) in the United Kingdom. The hSBA testing was performed at the GSK laboratory for all time points in the study.

Serum bactericidal activity assay using rabbit complement (rSBA)

Functional antibody responses against the four vaccine serogroups (A, C, W-135 and Y) were evaluated according to the protocol using an in-house serum bactericidal activity assay developed by the Centres for Disease Control and Prevention (CDC), with baby rabbit serum as complement source (rSBA). For testing at the GSK laboratory, titres were expressed as the reciprocal of the dilution resulting in 50% inhibition. For testing at PHE, titres were expressed as the reciprocal of the last dilution resulting in at least 50% inhibition.

Serum bactericidal activity assay using human complement (hSBA)

Functional anti-meningococcal serogroup activity was also determined by a serum bactericidal assay based on the CDC protocol using human complement (hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY). The cut-off of the assay was a dilution of 1:4. Titres were expressed as the reciprocal of the dilution resulting in 50% inhibition.

Enzyme-Linked Immunosorbent Assay (ELISA)

Meningococcal serogroup A, C, W-135, and Y PS-specific immunoglobulin G (IgG) was measured by ELISA. The assay was based on the CDC protocol. The assay cut-off was 0.30 μg/ml for all serogroups.

The use of the clinical endpoint of 2 μg/ml for serogroups A and C was based on the correlate of protection proposed for the plain meningococcal serogroups A and C polysaccharide vaccines.

Statistical methods

The objective of this persistence assessment was a descriptive analysis of the antibody persistence one year after a booster vaccination of *Nimenrix* as compared to *Meningitec*. The primary analysis of antibody persistence following booster vaccination was done on the according-to-protocol (ATP) cohort for persistence at Month 60.

Percentages of subjects with titres/concentrations above proposed endpoints, with 95% confidence intervals (CIs) were calculated using standard methods. The rSBA, hSBA and anti-PS geometric mean antibody concentrations/titres (GMCs/GMTs), with 95% CIs for the four meningococcal serogroups were assessed for each vaccine. The distribution of antibody titres/concentrations at each time point was tabulated and presented using reverse cumulative curves.

Exploratory between group analyses in terms of immunogenicity by rSBA, hSBA and anti-PS antibody concentrations were also conducted.

Endpoints

The primary objective of study MenACWY-TT-048 EXT: 039 was to evaluate antibody persistence in terms of percentage of subjects with rSBA antibody titres ≥ 1:8 for each of the four serogroups up to four years following primary vaccination. The results related to this objective are presented in the CSR and Annexes for the Years 2, 3 and 4 time points of study MenACWY-TT-048 EXT: 039, which have been submitted previously. Evaluation of antibody persistence following a booster dose of MenACWY-TT was part of the secondary study objectives.

1.2.2. Results

Of the 1000 subjects vaccinated in primary study MenACWY-TT-039, 286 children were enrolled at Month 60 (239 children in the ACWY-TT group and 47 children in the MenCCRM group). A total of 286 subjects attended the persistence visit at Month 60 and completed the study. Of these, nine subjects were eliminated from the analysis based on the ATP cohort for persistence at Month 60 due to the following reasons: protocol deviations reported in the primary study MenACYW-TT-039 or in previous time points of study MenACWYTT- 048 EXT: 039 (four subjects), non-compliance with the blood sampling schedule (three subjects) or missing of essential serological data (two subjects). The ATP cohort for evaluating persistence up to one year post-booster dose (Year 5 or Month 60) included 231 children in the ACWY-TT group and 46 children in the MenCCRM group, respectively.

The demographic profile of the subjects in the ATP cohort for persistence at Month 60 was comparable between the two groups with respect to mean age, gender and racial distribution (see table below). Overall, the mean age at Month 60 was 72.9 months with a SD of 1.70. The male: female ratio was 1.05. All subjects but one were of White - Caucasian/ European heritage (99.6%).

Table 1. Summary of demographic characteristics (ATP cohort for persistence at Month 60)

		ACWY-TT N = 231		MenCCRM N = 46		Total N = 277	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at Month 60 (months)	Mean	72.9	-	73.0	-	72.9	-
	SD	1.68	-	1.80	-	1.70	-
	Median	73.0	-	72.0	-	73.0	-
	Minimum	70	-	71	-	70	-
	Maximum	79	-	77	-	79	-
Gender	Female	113	48.9	22	47.8	135	48.7
	Male	118	51.1	24	52.2	142	51.3
Race	White - Caucasian / European heritage	230	99.6	46	100	276	99.6
	Other	1	0.4	0	0.0	1	0.4

ACWY-TT = Pooled Co-ad and ACWY-TT groups from primary study 109670 (MenACWY-TT-039)
MenCCRM = Pooled MMRV and MenCCRM groups from primary study 109670 (MenACWY-TT-039)
N = number of subjects; n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
SD = Standard deviation
Other Race: European- African Heritage

It should be noted that the rSBA and anti-PS testing has been performed at a different laboratory at Months 36, 48, 49 and 60 (PHE assay) compared to the previous time points (GSK assay), which limits direct longitudinal comparison of the results of different time points. As a result, the tables presenting rSBA and anti-PS results for the analysis of antibody persistence at Month 60 only include the Month 36, Month 48, Month 49 and Month 60 time points.

Antibody persistence following booster vaccination in terms of rSBA

Twelve months after administration of a booster dose of MenACWY-TT, the percentage of subjects with rSBA titres ≥ 1:8 was 100% for serogroups A, W-135 and Y and 97.4% for serogroup C (see Table 2). In the MenCCRM group, the percentage of subjects with rSBA titres ≥ 1:8 was 6.5%, 97.8%, 4.3% and 23.9% for serogroups A, C, W-135 and Y, respectively.

The percentage of subjects in the ACWY-TT group with rSBA titres ≥ 1:128 was 99.1% for serogroups A, W-135 and Y and 78.4% for serogroup C. In the MenCCRM group, the percentage of subjects with rSBA titres ≥ 1:128 was 6.5%, 87.0%, 4.3% and 23.9%, for serogroups A, C, W-135 and Y, respectively.

For serogroup C, the percentage of subjects with rSBA titres ≥1:128 decreased from 100% in both groups at one month post-booster to 78.4% and 87.0% in the ACWY-TT and MenCCRM groups, respectively, at 12 months post-booster administration.

The rSBA GMTs decreased from one month to 12 months post-booster for all four serogroups in the ACWY-TT group and for serogroup C in the MenCCRM group, but remained above levels observed prior to administration of the booster dose (at 36 and 48 months post-primary vaccination).

Table 2. Percentage of subjects with rSBA titres equal to or above the cut-off values of 1:8 and 1:128 and GMTs at 36, 48, 49 and 60 months postprimary vaccination (ATP cohort for persistence at Month 60)

				≥ 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-TT	M36	219	134	**61.2**	54.4	67.7	49	**22.4**	17.0	28.5	**19.2**	15.4	23.9
		M48	227	169	**74.4**	68.3	80.0	140	**61.7**	55.0	68.0	**114.0**	82.8	157.0
		M49	225	225	**100**	98.4	100	225	**100**	98.4	100	**7220.0**	6450.0	8081.9
		M60	231	231	**100**	98.4	100	229	**99.1**	96.9	99.9	**978.9**	860.2	1114.0
	MenCCRM	M36	43	3	**7.0**	1.5	19.1	3	**7.0**	1.5	19.1	**5.3**	3.8	7.2
		M48	46	13	**28.3**	16.0	43.5	12	**26.1**	14.3	41.1	**17.8**	8.3	37.9
		M49	46	9	**19.6**	9.4	33.9	8	**17.4**	7.8	31.4	**10.0**	5.5	18.4
		M60	46	3	**6.5**	1.4	17.9	3	**6.5**	1.4	17.9	**5.4**	3.8	7.6
rSBA-MenC	ACWY-TT	M36	219	71	**32.4**	26.3	39.1	16	**7.3**	4.2	11.6	**8.7**	7.2	10.4
		M48	228	93	**40.8**	34.3	47.5	33	**14.5**	10.2	19.7	**12.2**	9.8	15.2
		M49	226	226	**100**	98.4	100	226	**100**	98.4	100	**4616.4**	4055.0	5255.6
		M60	231	225	**97.4**	94.4	99.0	181	**78.4**	72.5	83.5	**226.4**	183.7	279.0
	MenCCRM	M36	43	6	**14.0**	5.3	27.9	3	**7.0**	1.5	19.1	**5.8**	4.2	8.1
		M48	46	16	**34.8**	21.4	50.2	10	**21.7**	10.9	36.4	**13.2**	7.3	23.6
		M49	46	46	**100**	92.3	100	46	**100**	92.3	100	**3741.9**	2654.4	5274.9
		M60	46	45	**97.8**	88.5	99.9	40	**87.0**	73.7	95.1	**320.9**	201.1	512.2
rSBA-MenW-135	ACWY-TT	M36	219	116	**53.0**	46.1	59.7	76	**34.7**	28.4	41.4	**27.6**	20.6	36.9
		M48	228	115	**50.4**	43.8	57.1	91	**39.9**	33.5	46.6	**30.9**	22.8	41.8
		M49	226	226	**100**	98.4	100	226	**100**	98.4	100	**10996.7**	9612.6	12580.1
		M60	231	231	**100**	98.4	100	229	**99.1**	96.9	99.9	**1390.7**	1203.2	1607.3
	MenCCRM	M36	43	2	**4.7**	0.6	15.8	2	**4.7**	0.6	15.8	**5.0**	3.6	6.9
		M48	46	7	**15.2**	6.3	28.9	7	**15.2**	6.3	28.9	**7.9**	4.8	12.9
		M49	46	9	**19.6**	9.4	33.9	8	**17.4**	7.8	31.4	**10.0**	5.6	18.0
		M60	46	2	**4.3**	0.5	14.8	2	**4.3**	0.5	14.8	**4.7**	3.8	5.7
rSBA-MenY	ACWY-TT	M36	219	123	**56.2**	49.3	62.8	68	**31.1**	25.0	37.6	**25.2**	19.3	32.7
		M48	228	134	**58.8**	52.1	65.2	95	**41.7**	35.2	48.4	**37.4**	28.0	49.8
		M49	226	226	**100**	98.4	100	226	**100**	98.4	100	**4616.4**	4169.8	5111.0
		M60	231	231	**100**	98.4	100	229	**99.1**	96.9	99.9	**1071.1**	924.9	1240.5
	MenCCRM	M36	43	6	**14.0**	5.3	27.9	2	**4.7**	0.6	15.8	**5.9**	4.2	8.2
		M48	46	11	**23.9**	12.6	38.8	9	**19.6**	9.4	33.9	**10.2**	5.9	17.5
		M49	46	15	**32.6**	19.5	48.0	15	**32.6**	19.5	48.0	**15.1**	8.3	27.4
		M60	46	11	**23.9**	12.6	38.8	11	**23.9**	12.6	38.8	**13.4**	6.9	25.8

ACWY-TT = Pooled Co-ad and ACWY-TT groups from primary study 109670 (MenACWY-TT-039)
MenCCRM = Pooled MMRV and MenCCRM groups from primary study 109670 (MenACWY-TT-039)
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
M36 = Month 36, 36 months post-primary vaccination
M48 = Month 48, 48 months post-primary vaccination and pre-booster vaccination
M49 = Month 49, one month post-booster vaccination
M60 = Month 60, 12 months post-booster vaccination

Exploratory analyses suggested a higher percentage of subjects who reached the 1:8 and 1:128 thresholds at 12 months after administration of the booster dose in the ACWY-TT compared to the MenCCRM group for serogroups A, W-135 and Y (see table below). Exploratory analyses suggested no difference between groups in terms of persistence of PHE rSBA-MenC titres ≥1:8 or ≥1:128 or PHE rSBA GMTs for serogroup C at 12 months post-booster (see Tables 3 and 4).

Table 3. Difference between groups in percentage of subjects with PHE rSBA titres equal to or above the cut-off value of 1:8 and 1:128, 60 months after the primary vaccination (ATP cohort for persistence at Month 60)

								Difference in percentage (ACWY-TT minus MenCCRM)		
		ACWY-TT			MenCCRM			%	95% CI	
Antibody	Type	N	n	%	N	n	%		LL	UL
rSBA-MenA	1:8	231	231	100	46	3	6.5	93.48	82.47	97.76
	1:128	231	229	99.1	46	3	6.5	92.61	81.55	97.07
rSBA-MenC	1:8	231	225	97.4	46	45	97.8	-0.42	-4.01	8.85
	1:128	231	181	78.4	46	40	87.0	-8.60	-17.91	4.88
rSBA-MenW-135	1:8	231	231	100	46	2	4.3	95.65	85.44	98.80
	1:128	231	229	99.1	46	2	4.3	94.79	84.53	98.16
rSBA-MenY	1:8	231	231	100	46	11	23.9	76.09	62.04	86.10
	1:128	231	229	99.1	46	11	23.9	75.22	61.12	85.31

ACWY-TT = Pooled Co-ad and ACWY-TT groups from primary study 109670 (MenACWY-TT-039)
MenCCRM = Pooled MMRV and MenCCRM groups from primary study 109670 (MenACWY-TT-039)
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = Standardized asymptotic 95% confidence interval
LL = lower limit, UL = upper limit

Table 4. GMT ratios between groups for PHE rSBA-MenC, 60 months after the primary vaccination (ATP cohort for persistence at Month 60)

ACWY-TT		MenCCRM		GMT ratio (ACWY-TT / MenCCRM)		
					95% CI	
N	GMT	N	GMT	Value	LL	UL
231	226.4	46	320.9	0.71	0.42	1.18

ACWY-TT = Pooled Co-ad and ACWY-TT groups from primary study 109670 (MenACWY-TT-039)
MenCCRM = Pooled MMRV and MenCCRM groups from primary study 109670 (MenACWY-TT-039)
GMT = geometric mean antibody titre
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (ANOVA model - pooled variance)
LL = lower limit, UL = upper limit

Antibody persistence following booster vaccination in terms of hSBA

Twelve months after administration of a booster dose of MenACWY-TT, the percentage of subjects with hSBA titres ≥ 1:8 was 100% for serogroups C, W-135 and Y and 95.5% for serogroup A (see table below). In the MenCCRM group, the percentage of subjects with hSBA titres ≥ 1:8 was 10.7%, 100%, 16.1% and 32.3% for serogroups A, C, W-135 and Y, respectively.

The hSBA GMTs decreased from one month to 12 months post-booster for all four serogroups in the ACWY-TT group and for serogroup C in the MenCCRM group, but remained above levels observed prior to administration of the booster dose.

Table 5. Percentage of subjects with hSBA titres equal to or above the cut-off values of 1:4 and 1:8 and GMTs (ATP cohort for persistence at Month 60)

				≥ 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-TT	PRE	226	4	**1.8**	0.5	4.5	1	**0.4**	0.0	2.4	**2.0**	2.0	2.1
		POST	220	185	**84.1**	78.6	88.7	178	**80.9**	75.1	85.9	**23.7**	19.5	28.7
		M24	191	52	**27.2**	21.0	34.1	47	**24.6**	18.7	31.3	**4.1**	3.4	4.9
		M36	210	77	**36.7**	30.1	43.6	72	**34.3**	27.9	41.1	**5.6**	4.5	6.8
		M48	203	56	**27.6**	21.6	34.3	55	**27.1**	21.1	33.8	**4.6**	3.7	5.5
		M49	214	213	**99.5**	97.4	100	213	**99.5**	97.4	100	**1371.2**	1149.7	1635.4
		M60	221	211	**95.5**	91.8	97.8	211	**95.5**	91.8	97.8	**88.0**	73.6	105.1
	MenCCRM	PRE	35	0	**0.0**	0.0	10.0	0	**0.0**	0.0	10.0	**2.0**	2.0	2.0
		POST	34	0	**0.0**	0.0	10.3	0	**0.0**	0.0	10.3	**2.0**	2.0	2.0
		M24	30	2	**6.7**	0.8	22.1	0	**0.0**	0.0	11.6	**2.1**	1.9	2.3
		M36	29	5	**17.2**	5.8	35.8	4	**13.8**	3.9	31.7	**2.7**	2.1	3.4
		M48	29	4	**13.8**	3.9	31.7	4	**13.8**	3.9	31.7	**2.8**	2.0	3.9
		M49	30	4	**13.3**	3.8	30.7	4	**13.3**	3.8	30.7	**2.7**	2.0	3.6
		M60	28	3	**10.7**	2.3	28.2	3	**10.7**	2.3	28.2	**2.5**	1.9	3.2
hSBA-MenC	ACWY-TT	PRE	230	2	**0.9**	0.1	3.1	2	**0.9**	0.1	3.1	**2.0**	2.0	2.1
		POST	219	215	**98.2**	95.4	99.5	214	**97.7**	94.8	99.3	**181.5**	154.5	213.2
		M24	181	157	**86.7**	80.9	91.3	155	**85.6**	79.7	90.4	**48.7**	37.5	63.1
		M36	211	168	**79.6**	73.5	84.8	162	**76.8**	70.5	82.3	**33.3**	25.5	43.5
		M48	211	153	**72.5**	66.0	78.4	152	**72.0**	65.5	78.0	**30.1**	22.4	40.5
		M49	221	221	**100**	98.3	100	221	**100**	98.3	100	**15490.7**	13389.3	17921.9
		M60	228	228	**100**	98.4	100	228	**100**	98.4	100	**1342.3**	1134.6	1588.1
	MenCCRM	PRE	35	1	**2.9**	0.1	14.9	1	**2.9**	0.1	14.9	**2.1**	1.9	2.3
		POST	34	28	**82.4**	65.5	93.2	28	**82.4**	65.5	93.2	**43.5**	23.6	80.2
		M24	26	13	**50.0**	29.9	70.1	11	**42.3**	23.4	63.1	**8.1**	4.1	15.7
		M36	29	11	**37.9**	20.7	57.7	11	**37.9**	20.7	57.7	**5.6**	3.3	9.6
		M48	33	15	**45.5**	28.1	63.6	15	**45.5**	28.1	63.6	**10.7**	4.8	23.8
		M49	35	35	**100**	90.0	100	35	**100**	90.0	100	**8474.8**	5787.3	12410.2
		M60	33	33	**100**	89.4	100	33	**100**	89.4	100	**931.1**	572.8	1513.4
hSBA-MenW-135	ACWY-TT	PRE	227	1	**0.4**	0.0	2.4	1	**0.4**	0.0	2.4	**2.0**	2.0	2.1
		POST	212	177	**83.5**	77.8	88.2	176	**83.0**	77.3	87.8	**47.7**	37.4	60.9
		M24	190	176	**92.6**	87.9	95.9	173	**91.1**	86.1	94.7	**81.5**	64.9	102.5
		M36	212	173	**81.6**	75.7	86.6	173	**81.6**	75.7	86.6	**53.6**	41.7	69.0
		M48	171	139	**81.3**	74.6	86.8	138	**80.7**	74.0	86.3	**48.3**	36.9	63.4
		M49	203	203	**100**	98.2	100	203	**100**	98.2	100	**13996.3**	12637.4	15501.3
		M60	218	218	**100**	98.3	100	218	**100**	98.3	100	**2196.6**	1955.7	2467.2
	MenCCRM	PRE	35	0	**0.0**	0.0	10.0	0	**0.0**	0.0	10.0	**2.0**	2.0	2.0
		POST	34	1	**2.9**	0.1	15.3	1	**2.9**	0.1	15.3	**2.2**	1.8	2.6
		M24	30	0	**0.0**	0.0	11.6	0	**0.0**	0.0	11.6	**2.0**	2.0	2.0
		M36	31	2	**6.5**	0.8	21.4	2	**6.5**	0.8	21.4	**2.4**	1.8	3.2
		M48	28	2	**7.1**	0.9	23.5	2	**7.1**	0.9	23.5	**2.6**	1.8	3.6
		M49	27	2	**7.4**	0.9	24.3	2	**7.4**	0.9	24.3	**2.7**	1.8	4.2
		M60	31	5	**16.1**	5.5	33.7	5	**16.1**	5.5	33.7	**3.4**	2.2	5.4

				≥ 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-TT	PRE	221	1	**0.5**	0.0	2.5	1	**0.5**	0.0	2.5	**2.0**	2.0	2.1
		POST	212	168	**79.2**	73.2	84.5	168	**79.2**	73.2	84.5	**30.8**	24.4	38.8
		M24	167	141	**84.4**	78.0	89.6	141	**84.4**	78.0	89.6	**55.4**	42.1	72.9
		M36	209	151	**72.2**	65.7	78.2	148	**70.8**	64.1	76.9	**32.5**	24.7	42.8
		M48	131	85	**64.9**	56.1	73.0	85	**64.9**	56.1	73.0	**29.9**	20.3	44.1
		M49	184	184	**100**	98.0	100	184	**100**	98.0	100	**6698.9**	5934.8	7561.3
		M60	206	206	**100**	98.2	100	206	**100**	98.2	100	**1110.8**	987.5	1249.6
	MenCCRM	PRE	35	1	**2.9**	0.1	14.9	1	**2.9**	0.1	14.9	**2.3**	1.7	3.0
		POST	34	1	**2.9**	0.1	15.3	1	**2.9**	0.1	15.3	**2.3**	1.7	3.2
		M24	27	5	**18.5**	6.3	38.1	5	**18.5**	6.3	38.1	**4.2**	2.2	8.1
		M36	31	6	**19.4**	7.5	37.5	6	**19.4**	7.5	37.5	**4.3**	2.4	7.7
		M48	28	6	**21.4**	8.3	41.0	6	**21.4**	8.3	41.0	**4.3**	2.4	7.8
		M49	27	7	**25.9**	11.1	46.3	7	**25.9**	11.1	46.3	**5.4**	2.7	11.0
		M60	31	10	**32.3**	16.7	51.4	10	**32.3**	16.7	51.4	**7.5**	3.6	15.7

ACWY-TT = Pooled Co-ad and ACWY-TT groups from primary study 109670 (MenACWY-TT-039)
MenCCRM = Pooled MMRV and MenCCRM groups from primary study 109670 (MenACWY-TT-039)
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Day 0, pre-primary vaccination
POST = Day 42, 42 days post-primary vaccination with meningococcal vaccine
M24 = Month 24, 24 months post-primary vaccination
M36 = Month 36, 36 months post-primary vaccination
M48 = Month 48, 48 months post-primary vaccination and pre-booster vaccination
M49 = Month 49, one month post-booster vaccination
M60 = Month 60, 12 months post-booster vaccination
Note: At the 'POST' time point the MMRV sub-group of the MenCCRM group did not yet receive a meningococcal vaccination

Exploratory analyses suggested a higher percentage of subjects who reached the 1:4 and 1:8 thresholds at 12 months after administration of the booster dose in the ACWY-TT compared to the MenCCRM group for serogroups A, W-135 and Y (see table below). Exploratory analyses suggested no difference between groups in terms of persistence of hSBA-MenC titres ≥1:4 or ≥1:8 or hSBA GMTs for serogroup C at 12 months post-booster (see Tables 6 and 7).

Table 6. Difference between groups in percentage of subjects with hSBA titres equal to or above the cut-off value of 1:4 and 1:8, 60 months after the primary vaccination (ATP cohort for persistence at Month 60)

								Difference in percentage (ACWY-TT minus MenCCRM)		
		ACWY-TT			MenCCRM			%	95% CI	
Antibody	Type	N	n	%	N	n	%		LL	UL
hSBA-MenA	1:4	221	211	95.5	28	3	10.7	84.76	68.05	92.38
	1:8	221	211	95.5	28	3	10.7	84.76	68.05	92.38
hSBA-MenC	1:4	228	228	100	33	33	100	0.00	-1.66	10.46
	1:8	228	228	100	33	33	100	0.00	-1.66	10.46
hSBA-MenW-135	1:4	218	218	100	31	5	16.1	83.87	67.33	92.92
	1:8	218	218	100	31	5	16.1	83.87	67.33	92.92
hSBA-MenY	1:4	206	206	100	31	10	32.3	67.74	50.10	81.45
	1:8	206	206	100	31	10	32.3	67.74	50.10	81.45

ACWY-TT = Pooled Co-ad and ACWY-TT groups from primary study 109670 (MenACWY-TT-039)
MenCCRM = Pooled MMRV and MenCCRM groups from primary study 109670 (MenACWY-TT-039)
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = Standardized asymptotic 95% confidence interval
LL = lower limit, UL = upper limit

Table 7. GMT ratios between groups for hSBA-MenC, 60 months after the primary vaccination (ATP cohort for persistence at Month 60)

ACWY-TT		MenCCRM		GMT ratio (ACWY-TT / MenCCRM)		
					95% CI	
N	GMT	N	GMT	Value	LL	UL
228	1342.3	33	931.1	1.44	0.90	2.32

ACWY-TT = Pooled Co-ad and ACWY-TT groups from primary study 109670 (MenACWY-TT-039)
MenCCRM = Pooled MMRV and MenCCRM groups from primary study 109670 (MenACWY-TT-039)
GMT = geometric mean antibody titre
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (ANOVA model - pooled variance)
LL = lower limit, UL = upper limit

Antibody persistence following booster vaccination in terms of polysaccharide antibody concentrations

Twelve months after administration of a booster dose of MenACWY-TT, the percentage of subjects with anti-PS concentrations ≥ 2 μg/mL was 83.7%, 44.7%, 100% and 98.8% for serogroups A, C, W-135 and Y, respectively (see table below). In the MenCCRM group, the percentage of subjects with anti-PS concentrations ≥ 2 μg/mL was 22.7%, 71.4%, 0.0% and 50.0% for the respective serogroups.

Table 8. Percentage of subjects with anti-PS concentrations equal to or above the cut-off values of 0.3 microgram/mL and 2.0 microgram/mL and GMCs at 36, 48, 49 and 60 months post-primary vaccination (ATP cohort for persistence at Month 60)

				≥ 0.3 µg/mL				≥ 2 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**Value**	**LL**	**UL**
Anti-PSA	ACWY-TT	M36	105	103	**98.1**	93.3	99.8	17	**16.2**	9.7	24.7	**1.07**	0.91	1.25
		M48	52	52	**100**	93.2	100	25	**48.1**	34.0	62.4	**2.00**	1.56	2.56
		M49	69	69	**100**	94.8	100	68	**98.6**	92.2	100	**13.13**	10.80	15.98
		M60	98	98	**100**	96.3	100	82	**83.7**	74.8	90.4	**4.22**	3.64	4.88
	MenCCRM	M36	24	20	**83.3**	62.6	95.3	3	**12.5**	2.7	32.4	**0.79**	0.52	1.20
		M48	22	20	**90.9**	70.8	98.9	9	**40.9**	20.7	63.6	**1.65**	0.97	2.83
		M49	16	16	**100**	79.4	100	7	**43.8**	19.8	70.1	**1.81**	1.17	2.81
		M60	22	22	**100**	84.6	100	5	**22.7**	7.8	45.4	**1.41**	1.09	1.82
Anti-PSC	ACWY-TT	M36	97	30	**30.9**	21.9	41.1	1	**1.0**	0.0	5.6	**0.22**	0.19	0.24
		M48	55	16	**29.1**	17.6	42.9	3	**5.5**	1.1	15.1	**0.25**	0.19	0.34
		M49	72	72	**100**	95.0	100	69	**95.8**	88.3	99.1	**8.57**	7.13	10.30
		M60	85	85	**100**	95.8	100	38	**44.7**	33.9	55.9	**1.81**	1.56	2.11
	MenCCRM	M36	23	5	**21.7**	7.5	43.7	1	**4.3**	0.1	21.9	**0.20**	0.15	0.26
		M48	21	7	**33.3**	14.6	57.0	3	**14.3**	3.0	36.3	**0.31**	0.18	0.54
		M49	19	19	**100**	82.4	100	19	**100**	82.4	100	**12.56**	8.83	17.87
		M60	14	13	**92.9**	66.1	99.8	10	**71.4**	41.9	91.6	**2.93**	1.47	5.86
Anti-PSW-135	ACWY-TT	M36	100	95	**95.0**	88.7	98.4	11	**11.0**	5.6	18.8	**0.76**	0.65	0.88
		M48	55	55	**100**	93.5	100	5	**9.1**	3.0	20.0	**0.85**	0.74	0.99
		M49	71	71	**100**	94.9	100	71	**100**	94.9	100	**59.41**	49.96	70.65
		M60	98	98	**100**	96.3	100	98	**100**	96.3	100	**9.44**	8.29	10.74
	MenCCRM	M36	23	11	**47.8**	26.8	69.4	0	**0.0**	0.0	14.8	**0.25**	0.19	0.32
		M48	22	17	**77.3**	54.6	92.2	0	**0.0**	0.0	15.4	**0.35**	0.28	0.46
		M49	20	13	**65.0**	40.8	84.6	0	**0.0**	0.0	16.8	**0.32**	0.23	0.45
		M60	22	8	**36.4**	17.2	59.3	0	**0.0**	0.0	15.4	**0.26**	0.18	0.37
Anti-PSY	ACWY-TT	M36	83	81	**97.6**	91.6	99.7	13	**15.7**	8.6	25.3	**1.08**	0.93	1.25
		M48	49	47	**95.9**	86.0	99.5	7	**14.3**	5.9	27.2	**0.75**	0.62	0.92
		M49	66	65	**98.5**	91.8	100	65	**98.5**	91.8	100	**37.86**	29.59	48.44
		M60	86	85	**98.8**	93.7	100	85	**98.8**	93.7	100	**10.31**	8.64	12.29
	MenCCRM	M36	20	18	**90.0**	68.3	98.8	1	**5.0**	0.1	24.9	**0.55**	0.39	0.79
		M48	20	18	**90.0**	68.3	98.8	3	**15.0**	3.2	37.9	**0.83**	0.54	1.28
		M49	11	10	**90.9**	58.7	99.8	0	**0.0**	0.0	28.5	**0.56**	0.37	0.84
		M60	12	12	**100**	73.5	100	6	**50.0**	21.1	78.9	**2.24**	1.25	4.02

ACWY-TT = Pooled Co-ad and ACWY-TT groups from primary study 109670 (MenACWY-TT-039)
MenCCRM = Pooled MMRV and MenCCRM groups from primary study 109670 (MenACWY-TT-039)
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
M36 = Month 36, 36 months post-primary vaccination
M48 = Month 48, 48 months post-primary vaccination and pre-booster vaccination
M49 = Month 49, one month post-booster vaccination
M60 = Month 60, 12 months post-booster vaccination

Exploratory analyses suggested a higher percentage of subjects with anti-PS concentrations ≥ 2 µg/mL at 12 months after administration of the booster dose in the ACWY-TT compared to the MenCCRM group for serogroups A, W-135 and Y (see table below).

Exploratory analyses suggested a difference between groups in terms of anti-PS GMCs for serogroup C at 12 months post-booster, in favour of the MenCCRM group (see Tables 9 and 10).

Table 9. Difference between groups in percentage of subjects with anti-PS concentrations equal to or above the cut-off value of 0.3 microgram/mL and 2.0 microgram/mL, 60 months after the primary vaccination (ATP cohort for persistence at Month 60)

								Difference in percentage (ACWY-TT minus MenCCRM)		
		ACWY-TT			MenCCRM			%	95% CI	
Antibody	Type	N	n	%	N	n	%		LL	UL
Anti-PSA	0.3 µg/mL	98	98	100	22	22	100	0.00	-3.80	14.97
	2 µg/mL	98	82	83.7	22	5	22.7	60.95	38.80	75.72
Anti-PSC	0.3 µg/mL	85	85	100	14	13	92.9	7.14	1.26	31.63
	2 µg/mL	85	38	44.7	14	10	71.4	-26.72	-47.38	1.64
Anti-PSW-135	0.3 µg/mL	98	98	100	22	8	36.4	63.64	42.87	80.32
	2 µg/mL	98	98	100	22	0	0.0	100	85.03	100
Anti-PSY	0.3 µg/mL	86	85	98.8	12	12	100	-1.16	-6.34	23.32
	2 µg/mL	86	85	98.8	12	6	50.0	48.84	23.96	73.67

ACWY-TT = Pooled Co-ad and ACWY-TT groups from primary study 109670 (MenACWY-TT-039)
MenCCRM = Pooled MMRV and MenCCRM groups from primary study 109670 (MenACWY-TT-039)
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = Standardized asymptotic 95% confidence interval
LL = lower limit, UL = upper limit

Table 10. Table 11 GMC ratios between groups for anti-PSC concentrations, 60 months after the primary vaccination (ATP cohort for persistence at Month 60)

				GMC ratio (ACWY-TT / MenCCRM)		
ACWY-TT		MenCCRM			95% CI	
N	GMC	N	GMC	Value	LL	UL
85	1.81	14	2.93	0.62	0.40	0.97

ACWY-TT = Pooled Co-ad and ACWY-TT groups from primary study 109670 (MenACWY-TT-039)
MenCCRM = Pooled MMRV and MenCCRM groups from primary study 109670 (MenACWY-TT-039)
GMC = geometric mean antibody concentration
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMC ratio (ANOVA model - pooled variance)
LL = lower limit, UL = upper limit

1.2.3. Discussion

The data provided on the persistence of antibodies to Nimenrix polysaccharide antigens A, C, W-135 and Y at month 60 (12 months after a booster dose at 48 months) were provided and compared with the results from a smaller cohort immunised with Meningitec. The results show that persistence of antibodies at month 60 is maintained using three different assays. Of note, a drop in the percentage of subjects with anti-PS antibodies at 60 months was seen in both vaccine groups as compared with the titres at 49 months and this drop was more marked in the Nimenrix group leading also to lower levels of antibody to polysaccharide C in the Nimenrix group than in the Meningitec group when assayed using the ELISA. However, the correlate of protection is SBA and this showed no significant difference between the two vaccine groups. Overall the results demonstrate maintenance of detectable antibody levels to Nimenrix antigens at month 60 following a booster dose at 48 months and higher levels at month 60 than these seen pre-booster at month 36.

1.3. Clinical Safety aspects

1.3.1. Methods – analysis of data submitted

Serious adverse events

The investigator or his/her delegate among the study centre staff was responsible for the detection and documentation of events meeting the criteria and definition of an serious adverse event (SAE). Each subject's parent(s)/guardian(s) were instructed to contact the investigator immediately should they manifest any signs or symptoms they perceived as serious.

Only SAEs considered as related to study vaccination by the investigator or lack of vaccine efficacy were to be reported during the persistence phase (up to the Month 60 visit). In addition SAEs that were related to study participation (e.g., protocol-mandated procedures, invasive tests, a change from existing therapy) or a concurrent GSK medication were to be reported.

The investigator assessed the maximum intensity that occurred over the duration of the event for all SAEs reported during the study. The intensity of each SAE was assigned to one of the categories displayed in table below.

Table 11. Intensity scale for SAEs

Intensity	Description
1 (mild)	An SAE which was easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	An SAE which was sufficiently discomforting to interfered with normal everyday activities.
3 (severe)	An SAE which prevented normal, everyday activities. (In a young child, such an SAE would, for example, prevent attendance at school/ kindergarten/ a day-care centre and would cause the parents/ guardians to seek medical advice.)

Causality of SAEs was assessed by the investigator using the following question: Was there a reasonable possibility that the SAE might have been caused by the investigational product?

Study cohort evaluated

The primary analysis of safety was based on the Total cohort at Month 60, which included all subjects vaccinated in the primary study MenACWY-TT-039 that came back for the visit at Month 60.

1.3.2. Results

Overall Extent of Exposure

The number of subjects vaccinated in each group is presented in table below and represent the Total cohort at Month 60 that was to be used for the safety analysis.

Table 12. Number of subjects and doses evaluated for safety in study MenACWY-TT-048 EXT: 039 Y5

Study group	Vaccines	Age	Number of subjects / booster doses
ACWY-TT	MenACWY-TT and *Priorix Tetra*	12-23 months	239
	MenACWY-TT	60-69 months	
MenCCRM	*Meningitec* and *Priorix Tetra*	12-23 months	47
	Meningitec	60-69 months	

Demographic and Other Characteristics of Study Population

The demographic characteristics of the subjects in the Total cohort at Month 60 are summarised in the table below. The demographic profile with respect to mean age, gender and racial distribution was comparable between the two study groups. Overall, the mean age at Month 60 was 72.9 months (standard deviation [SD] = 1.70 months). The male: female ratio was 1.07. All but two subjects were of White - Caucasian/ European heritage (99.3%).

Table 13. Summary of demographic characteristics (Total cohort at Month 60)

		ACWY-TT N = 239		MenCCRM N = 47		Total N = 286	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at Month 60 (months)	Mean	72.9	-	72.9	-	72.9	-
	SD	1.68	-	1.83	-	1.70	-
	Median	73.0	-	72.0	-	73.0	-
	Minimum	70	-	70	-	70	-
	Maximum	79	-	77	-	79	-
Gender	Female	116	48.5	22	46.8	138	48.3
	Male	123	51.5	25	53.2	148	51.7
Race	White - Caucasian / European heritage	238	99.6	46	97.9	284	99.3
	Other	1	0.4	1	2.1	2	0.7

ACWY-TT = Pooled Co-ad and ACWY-TT groups from primary study 109670 (MenACWY-TT-039)
MenCCRM = Pooled MMRV and MenCCRM groups from primary study 109670 (MenACWY-TT-039)
N = number of subjects
n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
SD = Standard deviation
Other Race: European- African Heritage and White-West African

Analysis of Adverse Events

No deaths were reported during study MenACWY-TT-048 EXT: 039 (up to the Month 60 visit).

No SAEs considered as possibly related to vaccination by the investigator or as related to study participation or GSK concomitant medication nor any events related to lack of vaccine efficacy were reported during this study (up to the Month 60 visit).

None of the subjects declined attendance at the Month 60 visit due to a serious or non-serious adverse event experienced since administration of the booster dose at Month 48.

1.3.3. Discussion

No new safety signals have arisen from the data submitted for this variation. Therefore, it is also accepted that no update of the RMP and no SmPC changes are proposed in this variation.

2. Overall conclusion and impact on the benefit/risk balance

The evaluation of the need for a booster dose to maintain optimum circulating antibody levels to the four meningococcal serogroups of MenACWY-TT is an important scientific objective and the MAH continues to evaluate the immunogenicity and reactogenicity of a booster dose in different age groups. The need for a booster dose for Nimenrix has not yet been established and this is currently reflected in the SmPC.

The results of this study showed that antibody persistence in terms of percentage of subjects who retained protective rSBA-MenC titres up to 1 year after booster administration was high and similar in MenACWY-TT recipients and those receiving the licensed Meningitec control (97.4% and 97.8% in the ACWY-TT and Meningitec groups, respectively). At 1 year post-booster, all the subjects boosted with MenACWY-TT retained vaccine-induced rSBA antibody titre levels indicative of putative protective efficacy against the three other serogroups (MenA, MenW-135 and MenY). Overall, these clinical trial data continue to demonstrate serological evidence of protection and an acceptable safety profile for Nimenrix. The previously established benefit-risk profile of Nimenrix for active immunisation of individuals from 12 months of age against invasive meningococcal diseases caused by Neisseria meningitidis serogroup A, C, W-135 and Y continues to be favourable and the results from the data submitted for this variation does not change the current positive benefit: risk balance for Nimenrix.

The MAH continues to assess longer term immunogenicity and when further results are available intends to provide the data in support of a change/update to the SmPC. In this procedure no SmPC changes are proposed, which is accepted. No safety concerns emerge from this month 60 data.

3. Recommendations

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 requested		**Type**
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	II

Submission of results of a 5 year follow-up study of the pivotal phase III study MenACWY-TT-039. The study report was submitted in line with requirements of Article 46 of Regulation (EC) No 1901/2006. The requested variation proposed no amendments to the PI.