EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 September 2013
EMA/707671/2013
Committee for Medicinal Products for Human Use (CHMP)

Nimenrix

(meningococcal group a, c, w135 and y conjugate vaccine)

Procedure No. EMEA/H/C/002226/P46/0037

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

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

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1. Executive Summary

Nimenrix is a quadrivalent meningococcal polysaccharide conjugate vaccine composed of the capsular polysaccharides of *Neisseria meningitidis* serogroups A, C, W-135 and Y, each conjugated to tetanus toxoid (designated ACWY-TT in this report).

Nimenrix was authorised via the centralised procedure on 20th April 2012 for active immunisation of individuals from the age of 12 months and above against invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W-135 and Y. A single dose is recommended in all age groups. The need for booster doses remains to be established but can be anticipated from the experience thus far with MenC conjugates. In addition, due to the rapid waning of hSBA titres for MenA section 4.4 of the SmPC contains a statement regarding consideration of a further dose after 12 months or more have elapsed if the subject is likely to be at particular risk of MenA infection.

On June 12 2013 in accordance with Article 46 of Regulation (EC) No 1901/2006 the MAH submitted a final study report on **MenACWY-TT-032 [EXT027] Y5.**

- The primary phase of study MenACWY-TT-027, as well as annex reports for the Year 1 and 2 persistence time-points, were submitted as part of the initial MAA for Nimenrix.
- Further follow-up reports at the year 3 and 4 antibody persistence time-points were submitted and assessed in accordance with Article 46 of Regulation (EC) No 1901/2006 (**P46-009 and P46-014**).
- A type II variation (**EMEA/H/C/2226/II/009**) to update the SmPC with antibody persistence data up to 4 years after primary vaccination is currently under review (responses to the first RSI are expected September 2013). This submission includes the year 3 and 4 antibody persistence data of MenACWY-TT-027 (designated 030 and 031).

A variation application specifically to add the Year 5 antibody persistence data is not planned. The MAH states that, in accordance with Article 16(2) of Regulation (EC) No 726/2004, the data do not influence the benefit-risk balance for Nimenrix and therefore do not require further regulatory action.

2. Recommendation

- The assessor does not agree that the Y5 data from MenACWY-TT-032 have no implications for the SmPC and PL.
- The assessor proposes that the implications of these results should be taken into account as part of the ongoing variation II/009 and suggests and additional question that should be put to the Company in a second RSI after receipt and assessment of the responses to the first RSI.
- Please see Section V of this report for the conclusions and proposals.

3. Introduction

- MenACWY-TT-027 [EXT032] represents the follow-up to Year 5 of subjects who were initially enrolled into the primary study MenACWY-TT-027.
- The current submission represents the last time point planned in the protocol.
- The report contains the rSBA data only; the hSBA data will follow in an Annex.

- It is important to understand that the rSBA data at Y5 were generated by the UK HPA (PHE) Reference Laboratory and not by GSK.

4. Scientific Discussion

- In the initial application dossier the data were presented from **MenACWY-TT-027/028/029** (Finland). These data included antibody persistence at 12 and 24 months.
- The study stratified by age 1-<2 years, 2-<6 years and 6-< 11 years at the time of vaccination.
- Controls aged 1-<2 years received Meningitec [MenCCRM]; controls aged 2-< 11 years received unconjugated ACWY vaccine [Mencevax; MenPS].
- **The assessor summarises all the previous data in this report since this is relevant for the overall conclusions. However, the change in rSBA assay from GSK (higher titres) to HPA (much lower titres) must be noted (see below).**
- **The assessor also provides relevant data from two other studies for which the latest data were assessed under II/009 to complete the picture.**

Initial study MenACWY-TT-027 plus Y1 and Y2 data in studies 028/029

Children aged 1- <2 years

The study concluded non-inferiority of ACWY-TT vs. *Meningitec* for anti-MenC rSBA responses based on a lower 95% CI of -0.27% around the difference with titres ≥1:8 at month 1 post-vaccination.

Month 1 sample								Difference in percentage (ACWY<2 minus MenCCRM)		
		ACWY<2			MenCCRM				95% CI	
Antibody	**Cut-off**	**N**	**n**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**
rSBA-MenC	≥1:8	220	220	100	68	67	98.5	1.47	**-0.27**	7.89

Pre-vaccination rates for rSBA ≥1:8 in the ACWY-TT and *Meningitec* groups were 42.4% and 40.0%, respectively, for MenA, 39.4% and 31.1% for MenC, 28.4% and 38.7% for MenW-135 and 55.3% and 61.2% for MenY. At M1 almost all in the ACWY-TT group had rSBA titres ≥1:128 for each of the meningococcal groups and percentages with ≥1:128 and GMTs were significantly higher vs. controls.

At M24 rSBA-MenC titres ≥ 1:8 occurred for 93.9% to 99.5% in the ACWY-TT group vs. 73.1% in the *Meningitec* group while ≥ 1:128 was observed in 56% and 33% in respective vaccine groups. Percentages with rSBA titres ≥1:128 and GMTs against the four meningococcal groups were statistically significantly higher with ACWY-TT.

The hSBA data up to M12 (see table below) showed that < 5% of subjects were seropositive to each meningococcal group at D0. At M12, 93.5% to 98.3% of the ACWY-TT subjects had hSBA titres ≥ 1:8 for MenC, W-135 and Y but for hSBA-MenA the percentage was 20.4%. In the *Meningitec* group 53.1% had hSBA-MenC titres ≥ 1:8 but < 12% of these Finnish children had such titres to the other meningococcal groups. The M12 GMTs for the ACWY-TT subjects against MenC, W-135 and Y were 88.7, 225.1 and 105.1, respectively, but only 3.6 for MenA. In the *Meningitec* group, the hSBA-MenC GMT was 12.2.

Percentages of subjects with hSBA-MenW-135 and hSBA-MenY titres ≥ 1:4 and ≥ 1:8 and the GMTs were higher at M12 than at M1. Percentages with hSBA titres ≥ 1:4 and ≥ 1:8 and GMTs adjusted for

baseline titre for the four meningococcal groups were statistically significantly higher in the ACWY-TT group vs. the control group that received only *Meningitec*.

hSBA titres and GMTs - Age stratum 1-<2 years (ATP cohort for persistence Year 1)

			≥1:4				≥1:8				GMT		
					95% CI				95% CI			95% CI	
Group	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
hSBA-MenA													
ACWY<2	PRE	209	3	1.4	0.3	4.1	0	0.0	0.0	1.7	2.0	2.0	2.1
	PI(M1)	211	196	92.9	88.5	96.0	191	90.5	85.7	94.1	57.6	47.9	69.3
	PI(M12)	201	47	**23.4**	17.7	29.9	41	**20.4**	15.1	26.6	**3.6**	3.1	4.2
MenCCRM	PRE	66	3	4.5	0.9	12.7	3	4.5	0.9	12.7	2.2	2.0	2.4
	PI(M1)	63	3	4.8	1.0	13.3	2	3.2	0.4	11.0	2.2	1.9	2.5
	PI(M12)	63	3	4.8	1.0	13.3	2	3.2	0.4	11.0	2.2	2.0	2.4
hSBA-MenC													
ACWY<2	PRE	208	3	1.4	0.3	4.2	3	1.4	0.3	4.2	2.1	2.0	2.2
	PI(M1)	215	213	99.1	96.7	99.9	213	99.1	96.7	99.9	187.0	161.6	216.5
	PI(M12)	200	192	**96.0**	92.3	98.3	192	**96.0**	92.3	98.3	**88.7**	73.8	106.5
MenCCRM	PRE	65	1	1.5	0.0	8.3	1	1.5	0.0	8.3	2.1	1.9	2.3
	PI(M1)	66	48	72.7	60.4	83.0	48	72.7	60.4	83.0	22.0	14.3	33.8
	PI(M12)	64	34	53.1	40.2	65.7	34	53.1	40.2	65.7	12.2	7.6	19.5
hSBA-MenW-135													
ACWY<2	PRE	199	2	1.0	0.1	3.6	2	1.0	0.1	3.6	2.1	2.0	2.2
	PI(M1)	173	141	81.5	74.9	87.0	137	79.2	72.4	85.0	38.5	29.3	50.5
	PI(M12)	175	172	**98.3**	95.1	99.6	172	**98.3**	95.1	99.6	**225.1**	184.5	274.7
MenCCRM	PRE	62	3	4.8	1.0	13.5	2	3.2	0.4	11.2	2.2	2.0	2.4
	PI(M1)	56	1	1.8	0.0	9.6	1	1.8	0.0	9.6	2.1	2.0	2.2
	PI(M12)	62	3	4.8	1.0	13.5	3	4.8	1.0	13.5	2.4	1.9	3.0
hSBA-MenY													
ACWY<2	PRE	182	7	3.8	1.6	7.8	5	2.7	0.9	6.3	2.2	2.0	2.3
	PI(M1)	196	131	66.8	59.8	73.4	130	66.3	59.2	72.9	23.8	18.1	31.4
	PI(M12)	214	200	**93.5**	89.3	96.4	200	**93.5**	89.3	96.4	**105.1**	85.2	129.7
MenCCRM	PRE	55	2	3.6	0.4	12.5	0	0.0	0.0	6.5	2.1	2.0	2.2
	PI(M1)	57	3	5.3	1.1	14.6	3	5.3	1.1	14.6	2.5	1.9	3.2
	PI(M12)	68	8	11.8	5.2	21.9	8	11.8	5.2	21.9	3.2	2.3	4.4

Children aged 2- < 11 years

In the primary analysis the lower bound of the 95% CIs was > 1.0 in all cases and therefore the pre-defined criterion for non-inferiority of ACWY-TT vs. unconjugated ACWY in this age group was met.

Month 1 sample							**Difference in response rate (ACWY minus MenPS)**		
	ACWY-TT			**MenPS**				**95% CI**	
Antibody	**N**	**n**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**
rSBA-MenA	185	182	98.4	62	57	91.9	6.44	**1.15**	16.04
rSBA-MenC	212	200	94.3	69	56	81.2	13.18	**4.79**	24.32
rSBA-MenW-135	199	199	100	68	65	95.6	4.41	**1.51**	12.21
rSBA-MenY	219	217	99.1	70	58	82.9	16.23	**8.99**	26.78

At D0 about 57-68% had rSBA antibody titres ≥1:8 for each of the four meningococcal groups. At M1 the percentages with ≥1:128 ranged from 96.6 to 100% with no statistically significant differences but the GMTs for all four meningococcal groups were statistically significantly higher in the ACWY-TT group.

Up to M24 the percentages with rSBA titres ≥1:8 and ≥1:128 and the GMTs for each of the four meningococcal groups were statistically significantly higher for the ACWY-TT subjects.

The hSBA data up to M12 for the age stratum 6-< 11 years (hSBA data were not available for the 2-<6 years cohort) showed that pre-vaccination seropositivity rates were low for MenA and MenW-135 but were 25-35% for MenC and MenY.

At M12 > 95% of the ACWY-TT subjects had hSBA titres ≥ 1:8 for MenC, W-135 and Y compared to only 16.3% against MenA. However, in the *Mencevax* group the percentages with these titres were significantly lower for MenC, W and Y and numerically lower for MenA vs. the ACWY-TT group. At M12 the GMTs were significantly higher for the ACWY-TT group against MenC, W and Y and numerically higher for MenA vs. controls.

hSBA titres and GMTs - Age stratum 6-<11 years (ATP cohort for persistence Year 1)

			≥1:4				≥1:8				GMT		
					95% CI				95% CI			95% CI	
Group	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
hSBA-MenA													
ACWY≥6	PRE	105	2	1.9	0.2	6.7	1	1.0	0.0	5.2	2.1	2.0	2.2
	PI(M1)	105	85	81.0	72.1	88.0	84	80.0	71.1	87.2	53.4	37.3	76.2
	PI(M12)	104	19	18.3	11.4	27.1	17	16.3	9.8	24.9	3.5	2.7	4.4
PS 6-<11	PRE	36	2	5.6	0.7	18.7	2	5.6	0.7	18.7	2.2	1.9	2.5
	PI(M1)	35	9	25.7	12.5	43.3	9	25.7	12.5	43.3	4.1	2.6	6.5
	PI(M12)	35	4	11.4	3.2	26.7	2	5.7	0.7	19.2	2.5	1.9	3.3
hSBA-MenC													
ACWY≥6	PRE	109	32	29.4	21.0	38.8	32	29.4	21.0	38.8	4.7	3.6	6.2
	PI(M1)	101	90	89.1	81.3	94.4	90	89.1	81.3	94.4	155.8	99.3	244.3
	PI(M12)	105	100	**95.2**	89.2	98.4	100	**95.2**	89.2	98.4	**129.5**	95.4	175.9
PS 6-<11	PRE	35	9	25.7	12.5	43.3	9	25.7	12.5	43.3	4.4	2.7	7.2
	PI(M1)	38	15	39.5	24.0	56.6	15	39.5	24.0	56.6	13.1	5.4	32.0
	PI(M12)	31	10	32.3	16.7	51.4	10	32.3	16.7	51.4	7.7	3.5	17.3
hSBA-MenW-135													
ACWY≥6	PRE	95	10	10.5	5.2	18.5	10	10.5	5.2	18.5	3.0	2.3	3.8
	PI(M1)	103	98	95.1	89.0	98.4	98	95.1	89.0	98.4	133.5	99.9	178.4
	PI(M12)	103	103	**100**	96.5	100	103	**100**	96.5	100	**256.7**	218.2	301.9
PS 6-<11	PRE	30	2	6.7	0.8	22.1	2	6.7	0.8	22.1	2.6	1.8	3.7
	PI(M1)	35	12	34.3	19.1	52.2	12	34.3	19.1	52.2	5.8	3.3	9.9
	PI(M12)	31	4	12.9	3.6	29.8	4	12.9	3.6	29.8	3.4	2.0	5.8
hSBA-MenY													
ACWY≥6	PRE	75	22	29.3	19.4	41.0	21	28.0	18.2	39.6	5.3	3.6	7.8
	PI(M1)	89	75	84.3	75.0	91.1	74	83.1	73.7	90.2	95.1	62.4	145.1
	PI(M12)	106	105	**99.1**	94.9	100	105	**99.1**	94.9	100	**265.0**	213.0	329.6
PS 6-<11	PRE	24	8	33.3	15.6	55.3	8	33.3	15.6	55.3	6.1	3.0	12.6
	PI(M1)	32	14	43.8	26.4	62.3	14	43.8	26.4	62.3	12.5	5.6	27.7
	PI(M12)	36	12	33.3	18.6	51.0	12	33.3	18.6	51.0	9.3	4.3	19.9

Year 3 and 4 data from P46-009 and P46-014

MenACWY-TT-030 Year 3

The numbers reported on at Y3 were 185/228 from the group aged 1-2 years when vaccinated with Nimenrix and 201/228 from the group that was aged 2-11 years. In each of the control groups for the two age cohorts there were 38/76 followed up.

Subjects aged 1-< 2 years

The Y3 rSBA data showed that 90.8% (rSBA-MenC) to 98.9% (rSBA-MenW-135) in the ACWY<2 group had rSBA titres at least 1:8 and 97.3% MenCCRM subjects had rSBA-MenC titres at least 1:8.

Using this rSBA assay (GSK's assay) in the Y3 study population there was evidence of considerable natural acquisition of antibody to MenA, MenW and MenY as well as an increase in anti-MenC rSBA titres in the control group.

rSBA titres - age stratum 1-<2 years (ATP cohort for persistence Year 3).

				≥ 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<2	PRE	151	65	43.0	35.0	51.3	49	32.5	25.1	40.5	23.0	16.4	32.2
		PI(M1)	177	177	100	97.9	100	177	100	97.9	100	3787.4	3353.2	4277.8
		PI(M12)	174	172	98.9	95.9	99.9	170	97.7	94.2	99.4	974.4	831.0	1142.4
		PI(M24)	165	164	99.4	96.7	100	156	94.5	89.9	97.5	575.2	494.0	669.9
		PI(M36)	170	168	98.8	95.8	99.9	161	94.7	90.2	97.6	518.6	447.6	600.8
	MenCCRM	PRE	35	15	42.9	26.3	60.6	12	34.3	19.1	52.2	21.8	10.8	44.1
		PI(M1)	32	10	31.3	16.1	50.0	6	18.8	7.2	36.4	14.4	7.0	29.4
		PI(M12)	22	7	31.8	13.9	54.9	7	31.8	13.9	54.9	17.6	6.5	47.6
		PI(M24)	30	21	70.0	50.6	85.3	18	60.0	40.6	77.3	56.5	28.5	112.2
		PI(M36)	32	27	84.4	67.2	94.7	21	65.6	46.8	81.4	117.1	65.0	211.2
rSBA-MenC	ACWY<2	PRE	163	71	43.6	35.8	51.5	25	15.3	10.2	21.8	15.5	11.9	20.0
		PI(M1)	175	175	100	97.9	100	173	98.9	95.9	99.9	887.0	770.4	1021.2
		PI(M12)	169	169	100	97.8	100	123	72.8	65.4	79.3	223.5	192.2	259.8
		PI(M24)	171	171	100	97.9	100	102	59.6	51.9	67.1	141.2	120.3	165.6
		PI(M36)	174	158	90.8	85.5	94.7	87	50.0	42.3	57.7	125.1	96.7	162.0
	MenCCRM	PRE	34	12	35.3	19.7	53.5	4	11.8	3.3	27.5	12.0	6.9	20.9
		PI(M1)	36	36	100	90.3	100	33	91.7	77.5	98.2	727.6	478.7	1105.8
		PI(M12)	35	35	100	90.0	100	25	71.4	53.7	85.4	218.3	157.9	301.8
		PI(M24)	36	36	100	90.3	100	16	44.4	27.9	61.9	158.6	103.8	242.2
		PI(M36)	37	36	97.3	85.8	99.9	22	59.5	42.1	75.2	185.7	118.3	291.5
rSBA-MenW-135	ACWY<2	PRE	167	50	29.9	23.1	37.5	32	19.2	13.5	26.0	11.7	9.0	15.1
		PI(M1)	177	177	100	97.9	100	177	100	97.9	100	5563.5	4976.9	6219.4
		PI(M12)	176	176	100	97.9	100	173	98.3	95.1	99.6	904.9	792.5	1033.2
		PI(M24)	173	172	99.4	96.8	100	158	91.3	86.1	95.1	439.3	379.0	509.4
		PI(M36)	174	172	98.9	95.9	99.9	151	86.8	80.8	91.4	439.8	370.5	522.0
	MenCCRM	PRE	33	11	33.3	18.0	51.8	7	21.2	9.0	38.9	12.6	6.8	23.5
		PI(M1)	36	14	38.9	23.1	56.5	10	27.8	14.2	45.2	17.5	9.2	33.6
		PI(M12)	35	22	62.9	44.9	78.5	12	34.3	19.1	52.2	37.9	20.1	71.3
		PI(M24)	30	15	50.0	31.3	68.7	7	23.3	9.9	42.3	22.9	11.6	45.1
		PI(M36)	33	24	72.7	54.5	86.7	14	42.4	25.5	60.8	64.5	33.5	124.3
rSBA-MenY	ACWY<2	PRE	166	96	57.8	49.9	65.4	66	39.8	32.3	47.6	37.4	27.4	51.0
		PI(M1)	177	177	100	97.9	100	176	99.4	96.9	100	2875.6	2540.0	3255.6
		PI(M12)	176	175	99.4	96.9	100	169	96.0	92.0	98.4	799.2	683.3	934.7
		PI(M24)	171	168	98.2	95.0	99.6	153	89.5	83.9	93.6	532.8	439.7	645.6
		PI(M36)	177	174	98.3	95.1	99.6	155	87.6	81.8	92.0	583.2	479.0	709.9

				≥ 1:8				≥ 1:128				GMT		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
	MenCCRM	PRE	36	24	66.7	49.0	81.4	16	44.4	27.9	61.9	52.5	26.7	103.3
		PI(M1)	36	29	80.6	64.0	91.8	20	55.6	38.1	72.1	101.5	54.3	189.7
		PI(M12)	35	24	68.6	50.7	83.1	19	54.3	36.6	71.2	75.7	36.2	158.3
		PI(M24)	35	27	77.1	59.9	89.6	18	51.4	34.0	68.6	100.6	50.6	200.0
		PI(M36)	36	33	91.7	77.5	98.2	21	58.3	40.8	74.5	176.0	97.6	317.3

ACWY<2 = MenACWY-TT (1-<2)
MenCCRM = *Meningitec* (1-<2)
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Pre-vaccination at Month 0
PI (M1) = Post-vaccination at Month 1
PI (M12) = Post-vaccination at Month 12
PI (M24) = Post-vaccination at Month 24
PI (M36) = Post-vaccination at Month 36

The hSBA results for children aged 1 to 2 years when vaccinated were also reported for Year 3.

Overall, at least 73.6% of the subjects vaccinated with MenACWY-TT had hSBA titres ≥ 1:8 for MenC, W-135 and Y but only 21.8% and 17.6% had hSBA-MenA titres at least 1:4 and 1:8, respectively. In the MenCCRM group which had only received a MenC conjugate vaccine, 75.8% of subjects had hSBA-MenC titres at least 1:8.

Subjects aged 2-<11 years

At Y3 in the Nimenrix group more than 98% had rSBA titres at least 1:8 for each meningococcal group compared to 81.1% (rSBA-MenY) to 91.2% (rSBA-MenA) in the MenPS group.

rSBA titres - age stratum 2-<11 years (ATP cohort for persistence Year 3).

				≥ 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≥2	PRE	162	109	67.3	59.5	74.4	84	51.9	43.9	59.8	58.4	42.8	79.6
		PI(M1)	196	196	100	98.1	100	195	99.5	97.2	100	7513.7	6740.4	8375.7
		PI(M12)	196	195	99.5	97.2	100	195	99.5	97.2	100	2533.4	2211.6	2902.1
		PI(M24)	193	193	100	98.1	100	191	99.0	96.3	99.9	1352.7	1191.4	1535.7
		PI(M36)	192	192	100	98.1	100	190	99.0	96.3	99.9	1184.2	1054.2	1330.3
	MenPS	PRE	31	20	64.5	45.4	80.8	19	61.3	42.2	78.2	69.8	30.6	158.8
		PI(M1)	37	37	100	90.5	100	37	100	90.5	100	2244.3	1737.7	2898.6
		PI(M12)	36	34	94.4	81.3	99.3	32	88.9	73.9	96.9	576.2	334.8	991.7
		PI(M24)	35	33	94.3	80.8	99.3	28	80.0	63.1	91.6	240.1	149.5	385.7
		PI(M36)	34	31	91.2	76.3	98.1	27	79.4	62.1	91.3	218.8	128.9	371.5
rSBA-MenC	ACWY≥2	PRE	184	118	64.1	56.7	71.1	55	29.9	23.4	37.1	36.5	27.8	48.0
		PI(M1)	196	196	100	98.1	100	195	99.5	97.2	100	2524.9	2162.1	2948.5
		PI(M12)	195	195	100	98.1	100	178	91.3	86.4	94.8	509.4	439.4	590.6
		PI(M24)	195	195	100	98.1	100	150	76.9	70.4	82.6	273.1	229.3	325.1
		PI(M36)	192	189	98.4	95.5	99.7	140	72.9	66.0	79.1	244.3	200.8	297.3
	MenPS	PRE	35	26	74.3	56.7	87.5	18	51.4	34.0	68.6	61.3	31.4	119.7
		PI(M1)	37	37	100	90.5	100	37	100	90.5	100	1433.7	939.4	2188.0
		PI(M12)	34	34	100	89.7	100	29	85.3	68.9	95.0	437.6	282.9	676.8
		PI(M24)	37	37	100	90.5	100	25	67.6	50.2	82.0	237.9	144.0	393.0
		PI(M36)	37	31	83.8	68.0	93.8	25	67.6	50.2	82.0	163.5	83.8	319.2
rSBA-MenW-135	ACWY≥2	PRE	173	107	61.8	54.2	69.1	81	46.8	39.2	54.5	45.4	33.5	61.5
		PI(M1)	196	196	100	98.1	100	196	100	98.1	100	12158.8	10949.9	13501.1
		PI(M12)	196	196	100	98.1	100	194	99.0	96.4	99.9	3064.7	2692.8	3488.0
		PI(M24)	195	194	99.5	97.2	100	193	99.0	96.3	99.9	1324.4	1154.4	1519.4
		PI(M36)	196	196	100	98.1	100	192	98.0	94.9	99.4	1737.1	1503.8	2006.7
	MenPS	PRE	33	22	66.7	48.2	82.0	14	42.4	25.5	60.8	57.4	27.6	119.4
		PI(M1)	37	37	100	90.5	100	37	100	90.5	100	2602.6	1795.6	3772.4
		PI(M12)	37	37	100	90.5	100	36	97.3	85.8	99.9	587.0	411.3	837.9
		PI(M24)	34	30	88.2	72.5	96.7	25	73.5	55.6	87.1	182.8	104.0	321.2
		PI(M36)	35	29	82.9	66.4	93.4	21	60.0	42.1	76.1	112.9	59.9	212.6
rSBA-MenY	ACWY≥2	PRE	192	127	66.1	59.0	72.8	85	44.3	37.1	51.6	55.4	41.3	74.3
		PI(M1)	196	196	100	98.1	100	195	99.5	97.2	100	6655.7	6009.1	7372.0
		PI(M12)	196	196	100	98.1	100	195	99.5	97.2	100	2164.0	1924.2	2433.6
		PI(M24)	195	195	100	98.1	100	194	99.5	97.2	100	1556.4	1355.9	1786.6
		PI(M36)	195	195	100	98.1	100	195	100	98.1	100	1551.6	1381.2	1743.1

				≥ 1:8				≥ 1:128				GMT		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
	MenPS	PRE	34	19	55.9	37.9	72.8	14	41.2	24.6	59.3	37.2	17.3	80.4
		PI(M1)	37	37	100	90.5	100	37	100	90.5	100	1813.8	1235.6	2662.5
		PI(M12)	34	32	94.1	80.3	99.3	28	82.4	65.5	93.2	467.5	261.3	836.5
		PI(M24)	37	30	81.1	64.8	92.0	20	54.1	36.9	70.5	116.2	59.3	227.7
		PI(M36)	37	30	81.1	64.8	92.0	19	51.4	34.4	68.1	103.8	54.3	198.3

ACWY≥2 = MenACWY-TT (2-<11)
MenPS = *Mencevax* ACWY (2-<11)
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Pre-vaccination at Month 0
PI (M1) = Post-vaccination at Month 1
PI (M12) = Post-vaccination at Month 12
PI (M24) = Post-vaccination at Month 24
PI (M36) = Post-vaccination at Month 36

MenACWY-TT-031 Year 4

Serological assays were performed at the GSK Biologicals' central laboratory (for rSBA and hSBA) and also at the Health Protection Agency (HPA) for rSBA only. The results were presented separately.

The numbers followed at Y4 were 357 MenACWY-TT-primed subjects, 34 Meningitec-primed subjects and 32 Mencevax ACWY-primed subjects.

rSBA and hSBA as determined at GSK

Subjects aged 1-<2 years

- 91.2% (rSBA-MenC) to 97.8% (rSBA-MenA) in the Nimenrix group had titres ≥ 1:8 and 90.0% in the MenCCRM group had rSBA-MenC titres ≥ 1:8.
- 40.7% (hSBA-MenA) to 85.7% (hSBA-MenC) in the Nimenrix group had hSBA titres ≥ 1:4 and 77.4% in the MenCCRM group had hSBA-MenC titres ≥ 1:4.

Subjects aged 2-<11 years

- 96.8% or more in the Nimenrix group and 75.9% (rSBAMenW-135) to 89.7% (rSBA-MenC) in the MenPS group had rSBA titres ≥ 1:8.

rSBA measured at HPA

Subjects aged 1-<2 years

- 30.3% (rSBA-MenC) to 61.2% (rSBA-MenA) in the Nimenrix group had rSBA titres ≥ 1:8 and 25.8% in the MenCCRM group had rSBA-MenC titres ≥ 1:8.

Subjects aged 2-<11 years

- 50% (rSBA-MenC) to 90.4% (rSBA-MenW-135) in the Nimenrix group and 6.9% (rSBA-MenY) to 41.4% (rSBA-MenC) in the MenPS group had rSBA titres ≥ 1:8.
- No hSBA data were obtained.

NEW data in subjects followed to Year 5 in study 032

The numbers who presented for follow-up at year 5 were relatively low in both age cohorts as follows:

Synopsis Table 1: Study population - age stratum 1-<2 years (Total cohort Year 5)		
Number of subjects	**ACWY<2**	**MenCCRM**
Planned, N	228	76
Enrolled, N (Total cohort Year 5)	52	12
Completed, n (%)	52 (100)	12 (100)
Demographics	**ACWY<2**	**MenCCRM**
N (Total cohort Year 5)	52	12
Females:Males	22:30	7:5
Mean Age, months (SD)	79.0 (3.09)	79.6 (2.81)
White - Caucasian / European Heritage, n (%)	51 (98.1)	11 (91.7)

Synopsis Table 2: Study population - age stratum 2-<11 years (Total cohort Year 5)		
Number of subjects	**ACWY≥2**	**MenPS**
Planned, N	228	76
Enrolled, N (Total cohort Year 5)	99	13
Completed, n (%)	99 (100)	13 (100)
Demographics	**ACWY≥2**	**MenPS**
N (Total cohort Year 5)	99	13
Females:Males	51:48	8:5
Mean Age, months (SD)	134.8 (31.30)	142.0 (22.96)
White - Caucasian / European Heritage, n (%)	97 (98.0)	13 (100)

There were 240 subjects aged 1-<2 years and 197 subjects aged 2-<11 years who did not participate in the Year 5 visit. Most had rSBA-MenC titres < 1:8 at a previous time point and/or received an extra dose of a MenCC vaccine before the Year 5 visit (56.0% in the MenCCRM group, 71.8% in the MenPS group, 49.3% in the ACWY<2 group and 37.2% in the ACWY≥2 group).

It should be noted that Y5 antibody persistence data are reported using the rSBA HPA assay only.

Subjects aged 1-<2 years

At Y5 percentages with HPA rSBA-MenC ≥1:8 was 77.6% in the Nimenrix group and 63.6% in the MenCCRM group. Rates for MenA, MenW-135 and MenY were 73.5%, 34.7% and 42.9%, respectively, in the Nimenrix group.

Synopsis Table 3: Percentage of subjects with HPA rSBA titres equal to or above the cut-off values of 1:8 and 1:128 and GMTs from Month 48 to Month 60- age stratum 1-<2 years (ATP cohort for persistence Year 5)

				≥ 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<2	PI(M48)	45	29	64.4	48.8	78.1	15	33.3	20.0	49.0	35.1	19.4	63.4
		PI(M60)	49	36	73.5	58.9	85.1	18	36.7	23.4	51.7	37.4	22.1	63.2
	MenCCRM	PI(M48)	10	0	0.0	0.0	30.8	0	0.0	0.0	30.8	4.0	4.0	4.0
		PI(M60)	11	0	0.0	0.0	28.5	0	0.0	0.0	28.5	4.0	4.0	4.0
rSBA-MenC	ACWY<2	PI(M48)	45	44	97.8	88.2	99.9	22	48.9	33.7	64.2	109.7	62.7	192.0
		PI(M60)	49	38	77.6	63.4	88.2	21	42.9	28.8	57.8	48.9	28.5	84.0
	MenCCRM	PI(M48)	10	8	80.0	44.4	97.5	7	70.0	34.8	93.3	137.2	22.6	831.8
		PI(M60)	11	7	63.6	30.8	89.1	4	36.4	10.9	69.2	26.5	6.5	107.2
rSBA-MenW-135	ACWY<2	PI(M48)	45	27	60.0	44.3	74.3	21	46.7	31.7	62.1	50.8	24.0	107.6
		PI(M60)	49	17	34.7	21.7	49.6	12	24.5	13.3	38.9	18.2	9.3	35.3
	MenCCRM	PI(M48)	10	0	0.0	0.0	30.8	0	0.0	0.0	30.8	4.0	4.0	4.0
		PI(M60)	11	2	18.2	2.3	51.8	1	9.1	0.2	41.3	7.1	2.6	19.1
rSBA-MenY	ACWY<2	PI(M48)	45	28	62.2	46.5	76.2	20	44.4	29.6	60.0	44.9	22.6	89.3
		PI(M60)	49	21	42.9	28.8	57.8	15	30.6	18.3	45.4	20.6	10.9	39.2
	MenCCRM	PI(M48)	10	3	30.0	6.7	65.2	2	20.0	2.5	55.6	12.1	2.3	63.5
		PI(M60)	11	2	18.2	2.3	51.8	2	18.2	2.3	51.8	11.7	2.3	59.7

Subjects aged 2-<11 years

At year 5 percentages with rSBA-MenA, MenC, MenW-135 and MenY ≥1:8 were 90.8%, 90.8%, 78.6% and 78.6%, respectively, in the Nimenrix group and 15.4%, 100%, 0.0% and 7.7%, respectively, in the MenPS group.

Synopsis Table 4: Percentage of subjects with HPA rSBA titres equal to or above the cut-off values of 1:8 and 1:128 and GMTs from Month 48 to Month 60- age stratum 2-<11 years (ATP cohort for persistence Year 5)

				≥ 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≥2	PI(M48)	97	86	88.7	80.6	94.2	64	66.0	55.7	75.3	123.5	85.4	178.6
		PI(M60)	98	89	90.8	83.3	95.7	66	67.3	57.1	76.5	141.3	98.2	203.4
	MenPS	PI(M48)	13	1	7.7	0.2	36.0	0	0.0	0.0	24.7	5.0	3.1	7.9
		PI(M60)	13	2	15.4	1.9	45.4	0	0.0	0.0	24.7	4.7	3.7	6.0
rSBA-MenC	ACWY≥2	PI(M48)	97	96	99.0	94.4	100	55	56.7	46.3	66.7	118.3	86.0	162.8
		PI(M60)	98	89	90.8	83.3	95.7	45	45.9	35.8	56.3	79.7	56.0	113.3
	MenPS	PI(M48)	13	12	92.3	64.0	99.8	9	69.2	38.6	90.9	206.8	71.7	596.7
		PI(M60)	13	13	100	75.3	100	9	69.2	38.6	90.9	128.0	56.4	290.7
rSBA-MenW-135	ACWY≥2	PI(M48)	96	92	95.8	89.7	98.9	91	94.8	88.3	98.3	1031.4	731.0	1455.4
		PI(M60)	98	77	78.6	69.1	86.2	68	69.4	59.3	78.3	208.5	127.9	340.0
	MenPS	PI(M48)	13	2	15.4	1.9	45.4	2	15.4	1.9	45.4	8.4	2.8	25.7
		PI(M60)	13	0	0.0	0.0	24.7	0	0.0	0.0	24.7	4.0	4.0	4.0
rSBA-MenY	ACWY≥2	PI(M48)	96	85	88.5	80.4	94.1	74	77.1	67.4	85.0	216.8	147.3	319.1
		PI(M60)	98	77	78.6	69.1	86.2	65	66.3	56.1	75.6	143.3	88.0	233.4
	MenPS	PI(M48)	13	1	7.7	0.2	36.0	0	0.0	0.0	24.7	4.2	3.8	4.7
		PI(M60)	13	1	7.7	0.2	36.0	1	7.7	0.2	36.0	5.5	2.7	11.1

Other data of relevance (from II/009)

The data from study MenACWY-TT-032 over 5 years in children aged from 1-10 years when they received a single dose of Nimenrix should also be viewed in light of the data from long term follow up of:

- Children initially vaccinated when **aged 1-<2 years** in study **MenACWY-TT-039** and boosted at Year 4 in the follow-up study 048
- Children initially vaccinated when **aged 2-10 years** in study **MenACWY-TT-081** with antibody persistence (088) at up to 32 and 44 months

Results from these studies have been described in the initial assessment report on **II/009**.

MenACWY-TT-048 (ext 039)

Pre- and post-booster blood samples were tested for SBA using the **HPA rSBA** (as in the Y5 results in 032) and **GSK hSBA** assays.

Antibody persistence at Y3 and Y4

At Y4 the percentage with **rSBA** titres ≥1:8 for MenC was 40.4% in the ACWY-TT group and 35.6% in the *Meningitec* group. The percentage with **hSBA** titres ≥1:8 for MenC was 73.2% in the ACWY-TT group and 46.9% for *Meningitec*.

Percentages in the ACWY-TT group with **rSBA** titres ≥1:8 at Y4 were 74.1% MenA, 49.3% for MenW-135 and 58.2% for MenY. Corresponding percentages with **hSBA** ≥1:8 were 28.8%, 80.6% and 65.4%.

Persistence data at Y3 and Y4 in toddlers aged 12-23 months at vaccination in MenACWY-TT-039 (ATP persistence cohort adapted for each persistence time point)

				HPA rSBA							hSBA							
				≥ 8				GMT				≥ 8				GMT		
Serogroup	Group	Timing	N	n	%	95% CI		Value	95% CI		N	n	%	95% CI		Value	95% CI	
						LL	UL		LL	UL				LL	UL		LL	UL
A	ACWY-TT	PI(Y3)	262	157	59.9	53.7	65.9	19.3	15.7	23.6	251	90	35.9	29.9	42.1	5.8	4.8	7.0
		PI(Y4)	224	166	74.1	67.9	79.7	107.3	77.6	148.3	198	57	28.8	22.6	35.6	4.9	4.0	6.0
C	ACWY-TT	PI(Y3)	262	94	35.9	30.1	42.0	9.8	8.1	11.7	253	198	78.3	72.7	83.2	37.8	29.4	48.6
		PI(Y4)	225	91	40.4	34.0	47.2	12.3	9.8	15.3	209	153	73.2	66.7	79.1	32.0	23.8	43.0
	Meningitec	PI(Y3)	46	6	13.0	4.9	26.3	5.7	4.2	7.7	31	13	41.9	24.5	60.9	6.2	3.7	10.3
		PI(Y4)	45	16	35.6	21.9	51.2	13.5	7.4	24.5	32	15	46.9	29.1	65.3	11.3	4.9	25.6
W-135	ACWY-TT	PI(Y3)	261	130	49.8	43.6	56.0	24.9	19.2	32.4	254	209	82.3	77.0	86.8	52.0	41.4	65.2
		PI(Y4)	225	111	49.3	42.6	56.1	30.5	22.4	41.5	165	133	80.6	73.7	86.3	47.1	35.7	62.2
Y	ACWY-TT	PI(Y3)	262	141	53.8	47.6	60.0	22.3	17.6	28.4	250	180	72.0	66.0	77.5	33.2	25.9	42.5
		PI(Y4)	225	131	58.2	51.5	64.7	36.2	27.1	48.4	130	85	65.4	56.5	73.5	29.8	20.2	44.1

GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with results available
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PI(YX) = Post-vaccination I at Year X
* in study MenACWY-TT-048: MenACWY-TT = Pooled Co-ad and ACWY-TT groups from primary study MenACWY-TT-039; *Meningitec* = Pooled MMRV and MenCCRM groups from primary study MenACWY-TT-039

The rSBA data showed some seemingly anomalous findings for Y3 and Y4 for the MenA data and for the MenC data in the Meningitec group in that there were notable increases in percentages with titres at least 1:8 and GMTs in the 12-month period between sampling. In contrast, the hSBA data showed the expected small differences in titres over the Y3-Y4 period when the antibody decay curve would be expected to have reached a near plateau. There is no obvious explanation for the MenC rSBA titres in the Meningitec group but it could reflect the majority having titres near to the cut-off at Y3 and Y4 so that even very small differences in assay runs could result in a proportion flipping from negative to positive and *vice versa*. These observations are being pursued in the RSI for II/009.

The MenA **hSBA** titres decreased quite markedly post-vaccination as was expected from all prior data but there was a plateau effect observed between Y3 and Y4.

The post-booster HPA rSBA GMT for MenC increased from pre-boost by 371.0-fold in the ACWY-TT group and by 260.2-fold in the group that received *Meningitec.* **The post-booster hSBA** GMTs increased by 531.1-fold and 704.4-fold in respective groups. A robust booster response (using rSBA and hSBA) to the other meningococcal groups was observed in ACWY-TT-primed children.

Pre- and post-booster data in children vaccinated as toddlers with ACWY-TT or Meningitec MenACWY-TT-048(EXT-039) Y4

				HPA rSBA							hSBA							
				≥ 8				GMT				≥ 8				GMT		
Serogroup	Group	Timing	N	n	%	95% CI		Value	95% CI		N	n	%	95% CI		Value	95% CI	
						LL	UL		LL	UL				LL	UL		LL	UL
A	ACWY-TT	Pre-booster	212	158	74.5	68.1	80.2	111.9	80.3	156.1	187	54	28.9	22.5	35.9	4.8	3.9	5.9
		Post-booster	214	214	100	98.3	100	7173.3	6389.2	8053.5	202	201	99.5	97.3	100	1343.2	1119.3	1612.0
C	ACWY-TT	Pre-booster	213	85	39.9	33.3	46.8	12.1	9.6	15.2	200	146	73.0	66.3	79.0	31.2	23.0	42.2
		Post-booster	215	215	100	98.3	100	4511.9	3935.9	5172.3	209	209	100	98.3	100	15831.4	13625.8	18394.0
	Meningitec	Pre-booster	43	16	37.2	23.0	53.3	14.3	7.7	26.5	31	15	48.4	30.2	66.9	11.9	5.1	27.6
		Post-booster	43	43	100	91.8	100	3718.4	2596.0	5326.0	33	33	100	89.4	100	8646.1	5886.6	12699.3
W-135	ACWY-TT	Pre-booster	213	104	48.8	41.9	55.7	30.2	21.9	41.5	158	129	81.6	74.7	87.3	48.3	36.5	63.9
		Post-booster	215	215	100	98.3	100	10949.7	9531.4	12579.1	192	192	100	98.1	100	14411.2	12971.8	16010.2
Y	ACWY-TT	Pre-booster	213	124	58.2	51.3	64.9	37.3	27.6	50.4	123	81	65.9	56.8	74.2	30.2	20.2	45.0
		Post-booster	215	215	100	98.3	100	4585.3	4128.6	5092.5	173	173	100	97.9	100	6775.5	5961.3	7700.9

GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with results available
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
ACWY-TT = Pooled Co-ad and ACWY-TT groups from primary study MenACWY-TT-039; *Meningitec* = Pooled MMRV and MenCCRM groups from primary study MenACWY-TT-039

MenACWY-TT-088[EXT-081]

The samples obtained at months 32 and 44 from children initially vaccinated with Nimenrix or Menjugate when aged 2-10 years were assayed using the **HPA rSBA** and **GSK hSBA** assays.

At Month 44 the percentages with MenC **rSBA** titres ≥1:8 were 37.0% in the ACWY-TT group and 45.5% in the *Menjugat*e group. In the ACWY-TT group rSBA titres ≥1:8 occurred in 87.5% for MenA, 68.3% for MenW-135 and 62.4% for MenY. The observed MenA rSBA GMT in the ACWY-TT group increased from Year 3 to Year 4, although the 95% CIs for both time points overlapped.

At Month 44 the percentage of subjects with **hSBA** titres ≥1:8 for MenC was 76.8% in the ACWY-TT group and 64.5% in the *Menjugate* group. The observed MenC GMTs declined from Month 32 to Month 44 in both groups. The percentages with hSBA titres ≥8 in the ACWY-TT group were 55.1% for MenA, 80.5% for MenW-135 and 82.9% for MenY.

The percentage with hSBA titres ≥1:8 for MenA increased between Month 32 and Month 44 (no overlap of 95% CIs). This increase was unexpected and coincided with observations in the laboratory of higher than average discordance between past and present titres obtained for the validation of a new lot of human complement. GSK therefore undertook investigations to assess the cause of this apparent anomaly. Re-testing of samples under different conditions identified that the transition to the use of stackers during incubation in the orbital shaker led to an overestimation of titres, particularly low titres. In view of these findings the use of stackers has ceased and samples from study MenACWY-TT-088(EXT-081) M44 will be re-tested using methods (i.e. without stackers) consistent with those used at previous time points. This testing is on-going and will be the subject of an annex to the clinical study report.

The SmPC already includes the M12 GSK hSBA data from study MenACWY-TT-028 [EXT027] Y1 in children aged 6-10 years at vaccination. These data display low MenA titres at Y1 but high titres for the other meningococcal groups.

Month 32 and 44 persistence data in children aged 2-10 years at vaccination
MenACWY-TT-088(EXT-081) M32 and M44 (ATP persistence cohort)

				HPA rSBA							hSBA							
				≥ 8				GMT				≥ 8				GMT		
Serogroup	Group	Timing	N	n	%	95% CI		Value	95% CI		N	n	%	95% CI		Value	95% CI	
						LL	UL		LL	UL				LL	UL		LL	UL
A	ACWY-TT	PI(M32)	193	167	86.5	80.9	91.0	196.3	144.1	267.2	90	23	25.6	16.9	35.8	4.6	3.3	6.3
		PI(M44)	189	162	85.7	79.9	90.4	307.5	223.7	422.8	89	49	55.1	44.1	65.6	12.0	8.2	17.4
C	ACWY-TT	PI(M32)	192	124	64.6	57.4	71.3	34.8	26.0	46.4	90	86	95.6	89.0	98.8	75.9	53.4	107.9
		PI(M44)	189	70	37.0	30.1	44.3	14.5	10.9	19.2	82	63	76.8	66.2	85.4	36.4	23.1	57.2
	Menjugate	PI(M32)	69	53	76.8	65.1	86.1	86.5	47.3	158.1	33	30	90.9	75.7	98.1	82.2	34.6	195.8
		PI(M44)	66	30	45.5	33.1	58.2	31.0	16.6	58.0	31	20	64.5	45.4	80.8	38.8	13.3	113.2
W-135	ACWY-TT	PI(M32)	193	149	77.2	70.6	82.9	213.9	149.3	306.6	86	73	84.9	75.5	91.7	69.9	48.2	101.5
		PI(M44)	189	129	68.3	61.1	74.8	103.5	72.5	147.6	87	70	80.5	70.6	88.2	64.3	42.7	96.8
Y	ACWY-TT	PI(M32)	193	157	81.3	75.1	86.6	227.4	164.8	313.7	91	74	81.3	71.8	88.7	79.2	52.5	119.3
		PI(M44)	189	118	62.4	55.1	69.4	78.9	54.6	114.0	76	63	82.9	72.5	90.6	126.7	78.0	205.7

GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with results available
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PI(MX) = Post-vaccination I at Month X

Assessor's comment

New data from ACWY-TT-032 - the subject of this P46-050 submission:

The UK HPA (now PHE) rSBA assay is already recognised to provide much more conservative results than those reported with GSK's rSBA assay, which is no longer in use by the MAH. The new data at Y5 in limited numbers of subjects show that:

- Antibody persistence was better in the subjects who received Nimenrix when they were aged > 2 years compared to those who were aged 12-23 months when vaccinated.
- Titres at least 1:8 were from 35-78% in those vaccinated aged 12-23 months but 79-91% in those vaccinated when aged 2-10 years.
- While the hSBA data are awaited for the Year 5 samples, these HPA rSBA data suggest that either 2 doses in the second year of life should be considered and/or a booster dose should be considered to maintain circulating antibody levels to all four meningococcal groups (i.e. in addition to the current warning re considering this to maintain MenA titres.
- In this regard it should be noted that quadrivalent meningococcal conjugate vaccines may be used as part of a routine vaccination programme in some countries (if not now then in the foreseeable future), which will generate an element of herd immunity. However, if subjects are vaccinated on an individual basis then herd immunity will not come into the equation except perhaps for MenC (depending on where the subject resides).
- On this basis, and while the results of an ongoing study to compare 1 vs. 2 doses in the second year of life, it is difficult to mandate either 2 doses or a booster for children presenting for first vaccination aged 12-23 months. However, a warning along the lines already included for all age groups in respect of MenA seems to be warranted.
- The assessor proposes that the MAH should address this request as part of the ongoing variation II/009 since this matter is entirely relevant to the proposals made for the SmPC in this application and including an addition will minimise any delay. Ideally, the hSBA data should also be submitted for assessment and added to the SmPC if they are available in time.
- For the older age group the data are less of a concern and could be added to section 5.1 as proposed for all the other antibody persistence data proposed to be added under variation II/009.

Data from previous time points in this study

Apart from the hSBA MenA data, which are already reflected in sections 4.4 and 5.1 of the SmPC, the hSBA data generated at M12 in this study showed very good antibody persistence in children aged 1-<2 years or aged 6-<11 years when vaccinated.

However, at Year 4 the percentages with hSBA titres at least 1:8 in the initial 1-<2 years age group ranged from 41% for MenA to 86% for MenC. In addition, the more conservative HPA rSBA data at Year 4 gave percentages in this age group with titres at least 1:8 in the range 30-61%. These results support the proposals now made based on the Year 5 HPA rSBA data.

In contrast, percentages of children initially aged 2-10 years with Year 4 HPA rSBA titres at least 1:8 were in the range 50-90%.

Data of relevance from other studies

MenACWY-TT-048 showed that percentages with Year 4 HPA rSBA titres at least 1:8 were from 40-74% in those vaccinated when aged 1-< 2 years. The MAH's hSBA assay gave higher percentages with titres at least 1:8 except for MenA. These results underline that conclusion that rSBA and hSBA assays give conflicting results for MenA SBA antibody persistence regardless of the laboratory that generates the data. However, the Year 4 booster data show a very robust anamnestic response in this age cohort regardless of the assay applied to the sera.

MenACWY-TT-088 showed that percentages with M44 HPA rSBA titres at least 1:8 ranged from 37-88%. These data support a general conclusion that antibody persistence is much better in children who were at least 2 years old when they received a single priming dose.

5. Rapporteur's Overall Conclusion and Recommendation

Overall conclusion

The data show better antibody persistence in children aged at least 2 years when they received a single dose of Nimenrix vs. those aged 1-<2 years. Taken together, the Year 4-5 data across the studies reported above point to the need to consider advising either 2 doses in the second year of life (an ongoing study is examining this) or advising giving consideration to a booster dose within 4 years. However, it does not seem appropriate to mandate either approach given the influence of the circumstances of use. Therefore the MAH should:

- Discuss these data in responses to a point that will be added when issuing the second RSI for II/009 (responses to the first RSI are expected September 2013)
- Draft a paragraph for section 4.4 to address the uncertainties regarding longer-term protection that are raised by these data
- Supply the hSBA data if they become available in time and
- Add all the relevant data to section 5.1 of the SmPC as part of the updates proposed in II/009.

Recommendation

The MAH should note these recommendations, which will be followed up at the time of assessing the responses to the first RSI.