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

Nimenrix

meningococcal group a, c, w135 and y conjugate vaccine

Procedure nos: EMEA/H/C/002226/P46/044

EMEA/H/C/002226/P46/045 and

EMEA/H/C/002226/P46/047

Note

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

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1. Introduction

On 7 and 8 September 2015, the MAH submitted 3 paediatric clinical study reports in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. Each of these represented a follow-up report resulting from assessment of antibody persistence and/or responses to a booster dose several years after the primary vaccination.

A short critical expert overview has also been provided for each of the three submissions.

2. Scientific discussion

2.1. Information on the development program

In November 2013, a letter was sent to the EMA to inform about a delay in providing the clinical study reports for the MenACWY-TT-088 EXT081 M56 and EXT081 M68 data and to explain the reason for the delay. These data from EXT081 M56 and M68/69 (pre/post-boost) are submitted in parallel as follows:

MenACWY-TT-088 EXT081 M56 is a follow-up study at 56 months of the primary study MenACWY-TT-081. MenACWY-TT-081 was submitted as part of the initial MAA for Nimenrix.

MenACWY-TT-088 EXT081 M68 is a follow-up study at 68 months of the primary study MenACWY-TT-081. It includes a booster dose at M68 and data on post-boost immune responses at M69.

The third clinical study report submitted concerns a separate study:

MenACWY-TT-043 EXT036 Y5 represents the follow-up to Year 5 of children who were initially enrolled into **MenACWY-TT-036**. The primary phase study MenACWY-TT-036, as well as the follow-up study after 2 years (MenACWYTT 043 EXT 036 Y2) were submitted as part of the initial MAA for Nimenrix. The Year 3 and Year 4 follow-up data (MenACWY-TT-043 EXT036 Y3 & MenACWY-TT-043 EXT036 Y4) were submitted and assessed under Article 46 of Regulation (EC) No. 1901/2006 in April 2013 (art 46 reference P46/0034 & P46/0035).

A variation application consisting of the full relevant data package (i.e. containing several studies to update the SmPC with available persistence and booster data) is expected to be submitted by **December 2015.**

2.2. Information on the pharmaceutical formulation used in the studies

Nimenrix was developed specifically for use in children and adults. The same formulation and dose is used across the full age range approved.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted three reports as described above.

2.3.2. Clinical studies

Study 081 Children 2-10 years vs. Menjugate

The study was conducted in 2008-9 in France and Germany. In the original study 400 subjects were to be randomised in a 3:1 ratio to ACWY-TT or Menjugate. There was stratified enrolment to provide ~200 subjects aged 2-5 and ~200 aged 6-10 years, which was to provide power to meet the immunogenicity criterion of at least 85.6%. All 414 subjects enrolled and vaccinated completed the initial phase. The mean age was 5.6 years (3.5 and 7.8 years in the two age strata) with a balanced gender distribution. Almost all subjects were of European Caucasian descent.

Only rSBA functional antibody responses (assayed at GSK's laboratories) were reported from the initial study but hSBA data were planned to be generated in follow-up. Based on rSBA, non-inferiority of ACWY-TT vs. *Menjugate* was demonstrated for responses to MenC based on a lower bound of the 95% CI that was -5.25%, with virtually no difference in response rates between vaccines for each subset according to baseline MenC serostatus. Response rates to ACWY-TT for each meningococcal group were higher in the subsets seronegative at baseline (99-100%) compared to those seropositive at baseline (89-98%). In the *Menjugate* group some subjects fulfilled the criteria for a vaccine response to MenA, W or Y. This was especially noticeable for rSBA against MenW and MenY among those seronegative to these meningococcal groups at baseline.

Difference in rSBA response rates (ATP cohort for immunogenicity)

								Difference		
		ACWY-TT			MenCCRM				95% CI	
Antibody	**Pre-vaccination status**	**N**	**n**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**
rSBA-MenA	S-	121	120	99.2	41	4	9.8	89.42	-	-
	S+	105	94	89.5	26	4	15.4	74.14	-	-
	Total	226	214	**94.7***	67	8	11.9	82.75	72.43	89.23
rSBA-MenC	S-	138	138	100	48	48	100	0.00	-	-
	S+	130	116	89.2	44	40	90.9	-1.68	-	-
	Total	268	254	94.8	92	88	95.7	-0.88	**-5.25**	5.75
rSBA-MenW-135	S-	56	56	100	20	8	40.0	60.00	-	-
	S+	226	222	98.2	70	3	4.3	93.94	-	-
	Total	282	278	**98.6***	90	11	12.2	86.36	77.88	91.80
rSBA-MenY	S-	39	39	100	16	6	37.5	62.50	-	-
	S+	246	236	95.9	72	1	1.4	94.55	-	-
	Total	285	275	**96.5***	88	7	8.0	88.54	80.69	93.12

The supplementary tables of the response rates by age strata showed that in each case the responses to the MenC conjugates were comparable. In both age strata there were similar responses to MenW and MenY in Menjugate subjects who were seronegative for these groups at baseline. However, responses to MenA, W and Y were all much higher in the ACWY-TT group regardless of baseline serostatus.

As shown below:

- Baseline percentages with rSBA titres ≥ 1:8 ranged from 43.4% (MenA in the *Menjugate* group) to 86.3% (MenY in the ACWY-TT group).
- The percentages with rSBA titres ≥ 1:128 increased to at least 99.3% after administration of ACWY-TT and all the *Menjugate* subjects had a MenC titre ≥ 1:128.

- The rSBA GMTs increased by 54-fold to 198-fold in the ACWY-TT group and the MenC GMT increased 273-fold in the *Menjugate* group vs. 123-fold in the ACWY-TT group. The rSBA-MenC GMT adjusted for pre-vaccination measurements and age strata was statistically significantly lower in the ACWY-TT group.

rSBA titres ≥1:8 and 1:128 and GMTs (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-TT	PRE	227	106	46.7	40.1	53.4	92	40.5	34.1	47.2	31.5	23.3	42.5
		PI(M1)	294	293	**99.7**	98.1	100	293	**99.7**	98.1	100	**6236.1**	5574.5	6976.3
	MenCCRM	PRE	76	33	43.4	32.1	55.3	28	36.8	26.1	48.7	25.9	15.6	43.0
		PI(M1)	82	34	41.5	30.7	52.9	27	32.9	22.9	44.2	27.2	15.6	47.4
rSBA-MenC	ACWY-TT	PRE	270	131	48.5	42.4	54.7	64	23.7	18.8	29.2	22.7	18.1	28.4
		PI(M1)	293	293	100	98.7	100	291	99.3	97.6	99.9	**2794.8**	2393.5	3263.3
	MenCCRM	PRE	94	44	46.8	36.4	57.4	18	19.1	11.8	28.6	19.4	13.1	28.8
		PI(M1)	97	97	100	96.3	100	97	100	96.3	100	5291.6	3814.6	7340.5
rSBA-MenW-135	ACWY-TT	PRE	282	226	80.1	75.0	84.6	148	52.5	46.5	58.4	83.2	67.9	102.0
		PI(M1)	296	295	**99.7**	98.1	100	294	**99.3**	97.6	99.9	**8549.5**	7618.5	9594.3
	MenCCRM	PRE	92	72	78.3	68.4	86.2	43	46.7	36.3	57.4	70.2	48.5	101.6
		PI(M1)	95	76	80.0	70.5	87.5	45	47.4	37.0	57.9	87.3	58.5	130.4
rSBA-MenY	ACWY-TT	PRE	285	246	86.3	81.8	90.1	193	67.7	62.0	73.1	153.6	125.3	188.3
		PI(M1)	295	295	**100**	98.8	100	295	**100**	98.8	100	**8360.7**	7447.3	9386.1
	MenCCRM	PRE	90	73	81.1	71.5	88.6	51	56.7	45.8	67.1	107.4	71.4	161.6
		PI(M1)	95	77	81.1	71.7	88.4	56	58.9	48.4	68.9	128.2	83.8	196.2

The post-vaccination percentages with rSBA titres ≥ 1:8 and ≥ 1:128 were comparable for the two age strata whereas the GMTs tended to be lower in the younger subjects compared to the older subjects. In each age stratum of subjects who received the ACWY-TT vaccine the rSBA GMT for MenC was lower than for the other three meningococcal groups.

Difference in rSBA GMTs (ATP-I)

subjects 2-5 years of age					**Adjusted GMT ratio**		
	ACWY<6		**MenC<6**			**95% CI**	
Anti body	**N**	**Adjusted GMT**	**N**	**Adjusted GMT**	**Value**	**LL**	**UL**
rSBA-MenA	122	4879.4	35	13.4	364.35	232.28	571.51
rSBA-MenC	141	1952.0	50	4514.2	0.43	0.29	0.65
rSBA-MenW-135	153	7981.4	46	84.6	94.32	67.43	131.94
rSBA-MenY	150	6619.3	45	84.1	78.72	54.55	113.58

subjects 6-10 years of age					**Adjusted GMT ratio**		
	ACWY≥ 6		**MenC≥ 6**			**95% CI**	
Anti body	**N**	**Adjusted GMT**	**N**	**Adjusted GMT**	**Value**	**LL**	**UL**
rSBA-MenA	104	7308.1	32	47.1	155.06	81.18	296.19
rSBA-MenC	127	3646.9	42	6453.2	0.57	0.34	0.93
rSBA-MenW-135	129	8815.9	44	115.1	76.61	46.76	125.54
rSBA-MenY	135	10446.5	43	285.8	36.55	24.55	54.41

Percentages of subjects with anti-PS concentrations ≥ 0.3 μg/mL before vaccination were low for each meningococcal group (from 3.4% to 23.1%). One month after vaccination anti-PS ≥ 2 μg/ml was observed in at least 86.8% in the ACWY-TT group and all subjects in the *Menjugate* group had ≥ 2 μg/ml against MenC. GMCs increased from 41-fold to 162-fold after ACWY-TT and by 90-fold to MenC in *Menjugate* recipients compared to 83-fold in ACWY-TT recipients. No statistically significant difference was observed for GMCs adjusted for pre-vaccination measurements and age strata between the ACWY-TT group and the *Menjugate* group.

Anti-tetanus antibody was not reported from this study.

For the comparison with *Menjugate* the most frequently reported solicited local AE in both vaccine groups was redness for subjects 2-5 years of age and pain for subjects 6-10 years of age. There were no significant differences between groups for the AEs reported in the 2-5 and 6-10 years age groups. There were no SAEs reported in the primary vaccination phase of the study.

Ext 081 Month 56

The analysis of antibody persistence was based on the ATP cohort for antibody persistence at Month 56. Since >5% of those with Month 56 serological results were excluded from the ATP cohort a second analysis based on the Total Vaccinated Cohort Month 56 was performed. For each treatment group, at the Month 56 blood sampling time-point, and for each antigen assessed:

- GMTs with 95% confidence intervals (CIs) were tabulated.
- Percentages of subjects with titres above the proposed cut-offs with exact 95% CIs were calculated.
- The distribution of antibody titres was tabulated and presented using reverse cumulative curves.

All reported SAEs considered related to study procedures, or a concomitant GSK drug or vaccine, or fatal SAEs were to be described in detail from the end of the six-month Extended Safety Follow-up period following vaccination until the Month 56 persistence time-point.

Of the 414 subjects enrolled in MENACWY-TT-081 there were 260 enrolled at the Month 56 persistence time-point, including 193 from the ACWY-TT group and 67 from the MenCCRM group.

Synopsis Table 1: Study Population (Total cohort at Month 56)		
Number of subjects	**ACWY-TT**	**MenCCRM**
Planned, N	122	41
Enrolled in study 088, N (Total cohort at Month 56)	193	67
Completed Month 56, n (%)	193 (100)	67 (100)
Demographics	**ACWY-TT**	**MenCCRM**
N (Total cohort at Month 56)	193	67
Females:Males	98:95	31:36
Mean Age, years (SD)	10.4 (2.6)	10.1 (2.4)
Median Age, years (minimum, maximum)	10 (6, 15)	10 (6, 15)
White - Caucasian / European heritage, n (%)	165 (85.5)	58 (86.6)
White - Arabic / North African Heritage, n (%)	12 (6.2)	6 (9.0)
Other, n (%)	7 (3.6)	1 (1.5)

The rSBA serological testing at pre-vaccination and one month post-vaccination in MENACWY-TT-081 were performed at GSK laboratories but rSBA testing at Months 32, 44 and 56 were performed at the Public Health England (PHE) laboratories in the United Kingdom. Therefore rSBA antibody kinetics and decay from one month post-vaccination cannot be directly assessed and the table below shows the serial data from M32 onwards.

At Month 56 based on PHE rSBA data (see table below):

- Percentages with rSBA-MenA titres ≥1:8 were 86.6% in the ACWY-TT group and 29.2% in the MenCCRM group with rates at ≥1:128 of 57.5% vs. 15.4%.
- Percentages with rSBA-MenC titres ≥1:8 were 59.1% in the ACWY-TT group and 64.6% in the MenCCRM group with rates at ≥1:128 of 34.9% vs. 49.2%.
- Percentages with rSBA-MenW-135 titres ≥1:8 were 78.0% in the ACWY-TT group and 26.2% in the MenCCRM group with rates at ≥1:128 of 66.1% vs. 15.4%.

- Percentages with rSBA-MenY titres ≥1:8 were 80.1% in the ACWY-TT group and 21.9% in the MenCCRM group with rates at ≥1:128 of 74.7% vs. 15.6%.

Synopsis Table 2: Number and percentage of subjects with rSBA-MenA (PHE), rSBA-MenC (PHE), rSBA-MenW-135 (PHE) and rSBA-MenY (PHE) titres equal to or above 1:8 and 1:128 and GMTs (ATP cohort for persistence at Month 56)

				≥ 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	PI(M32)	179	157	87.7	82.0	92.1	132	73.7	66.7	80.0	205.3	149.9	281.2
		PI(M44)	181	154	85.1	79.0	89.9	143	79.0	72.3	84.7	295.0	212.1	410.2
		PI(M56)	186	161	86.6	80.8	91.1	107	57.5	50.1	64.7	120.1	87.0	165.9
	MenCCRM	PI(M32)	65	15	23.1	13.5	35.2	9	13.8	6.5	24.7	8.3	5.6	12.5
		PI(M44)	64	16	25.0	15.0	37.4	16	25.0	15.0	37.4	13.5	7.8	23.2
		PI(M56)	65	19	29.2	18.6	41.8	10	15.4	7.6	26.5	9.8	6.4	15.0
rSBA-MenC	ACWY-TT	PI(M32)	178	113	63.5	56.0	70.6	62	34.8	27.9	42.3	32.4	24.1	43.5
		PI(M44)	181	66	36.5	29.5	43.9	36	19.9	14.3	26.5	14.2	10.7	18.9
		PI(M56)	186	110	59.1	51.7	66.3	65	34.9	28.1	42.3	30.5	22.6	41.1
	MenCCRM	PI(M32)	65	50	76.9	64.8	86.5	34	52.3	39.5	64.9	94.0	50.1	176.2
		PI(M44)	64	30	46.9	34.3	59.8	23	35.9	24.3	48.9	33.1	17.4	62.6
		PI(M56)	65	42	64.6	51.8	76.1	32	49.2	36.6	61.9	69.0	36.9	128.9
rSBA-MenW-135	ACWY-TT	PI(M32)	179	139	77.7	70.8	83.5	129	72.1	64.9	78.5	238.8	164.6	346.4
		PI(M44)	181	125	69.1	61.8	75.7	117	64.6	57.2	71.6	110.2	76.7	158.5
		PI(M56)	186	145	78.0	71.3	83.7	123	66.1	58.8	72.9	158.3	112.4	222.9
	MenCCRM	PI(M32)	65	5	7.7	2.5	17.0	5	7.7	2.5	17.0	5.7	4.2	7.9
		PI(M44)	64	7	10.9	4.5	21.2	5	7.8	2.6	17.3	6.0	4.3	8.3
		PI(M56)	65	17	26.2	16.0	38.5	10	15.4	7.6	26.5	10.3	6.4	16.6
rSBA-MenY	ACWY-TT	PI(M32)	179	146	81.6	75.1	87.0	135	75.4	68.4	81.5	230.6	165.0	322.2
		PI(M44)	181	113	62.4	54.9	69.5	102	56.4	48.8	63.7	78.4	53.8	114.2
		PI(M56)	186	149	80.1	73.6	85.6	139	74.7	67.9	80.8	233.2	166.0	327.6
	MenCCRM	PI(M32)	65	10	15.4	7.6	26.5	8	12.3	5.5	22.8	7.5	5.1	11.1
		PI(M44)	64	4	6.3	1.7	15.2	3	4.7	1.0	13.1	5.0	3.9	6.3
		PI(M56)	64	14	21.9	12.5	34.0	10	15.6	7.8	26.9	9.0	6.0	13.6

Table 11 Number and percentage of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY titres equal to or above 1:4 and 1:8 and GMTs (ATP cohort for persistence at Month 56)

				≥ 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	PI(M32)	85	22	25.9	17.0	36.5	21	24.7	16.0	35.3	4.4	3.2	6.1
		PI(M44)	87	26	29.9	20.5	40.6	23	26.4	17.6	37.0	4.9	3.5	6.8
		PI(M56)	89	53	59.6	48.6	69.8	53	59.6	48.6	69.8	10.6	7.6	14.9
	MenCCRM	PI(M32)	31	4	12.9	3.6	29.8	4	12.9	3.6	29.8	2.6	2.0	3.4
		PI(M44)	30	5	16.7	5.6	34.7	5	16.7	5.6	34.7	2.8	2.1	3.7
		PI(M56)	33	19	57.6	39.2	74.5	19	57.6	39.2	74.5	7.6	5.0	11.8
hSBA-MenC	ACWY-TT	PI(M32)	85	82	96.5	90.0	99.3	82	96.5	90.0	99.3	75.2	52.9	107.0
		PI(M44)	81	62	76.5	65.8	85.2	62	76.5	65.8	85.2	36.3	22.9	57.4
		PI(M56)	86	66	76.7	66.4	85.2	64	74.4	63.9	83.2	20.6	13.8	30.8
	MenCCRM	PI(M32)	30	27	90.0	73.5	97.9	27	90.0	73.5	97.9	87.7	34.1	225.4
		PI(M44)	31	19	61.3	42.2	78.2	19	61.3	42.2	78.2	36.5	12.3	108.2
		PI(M56)	31	21	67.7	48.6	83.3	21	67.7	48.6	83.3	31.2	11.5	85.0
hSBA-MenW-135	ACWY-TT	PI(M32)	78	65	83.3	73.2	90.8	65	83.3	73.2	90.8	64.0	42.8	95.5
		PI(M44)	81	65	80.2	69.9	88.3	65	80.2	69.9	88.3	63.4	41.4	97.2
		PI(M56)	83	69	83.1	73.3	90.5	69	83.1	73.3	90.5	59.3	40.2	87.6
	MenCCRM	PI(M32)	21	3	14.3	3.0	36.3	3	14.3	3.0	36.3	3.3	1.8	6.2
		PI(M44)	29	7	24.1	10.3	43.5	7	24.1	10.3	43.5	4.8	2.6	8.9
		PI(M56)	30	13	43.3	25.5	62.6	13	43.3	25.5	62.6	9.2	4.7	18.2
hSBA-MenY	ACWY-TT	PI(M32)	83	67	80.7	70.6	88.6	67	80.7	70.6	88.6	80.7	52.2	124.9
		PI(M44)	70	58	82.9	72.0	90.8	58	82.9	72.0	90.8	133.6	80.3	222.2
		PI(M56)	89	79	88.8	80.3	94.5	79	88.8	80.3	94.5	117.9	80.8	171.9
	MenCCRM	PI(M32)	26	12	46.2	26.6	66.6	12	46.2	26.6	66.6	14.7	5.9	36.8
		PI(M44)	25	11	44.0	24.4	65.1	11	44.0	24.4	65.1	15.0	5.5	40.7
		PI(M56)	31	22	71.0	52.0	85.8	22	71.0	52.0	85.8	35.7	16.8	75.9

At Month 56 based on hSBA data (GSK's assay; see table above):

- Percentages with hSBA-MenA titres ≥1:8 were very similar for the ACWY-TT and MenCCRM groups (59.6% and 57.6%) but in both groups these rates were much higher than at M32 and M44 (<30% and < 20% for respective vaccine groups). Considering that the study sites were in France and Germany this finding is rather strange. However, in both groups the GMTs were low and not markedly higher than at the two previous time points, suggesting that in reality the difference over time reflects only a shift in percentages with titres just below and just above the assay LLOQ. No details are provided on the hSBA assay.

- Percentages with hSBA-MenC titres ≥1:8 were 74.4% in the ACWY-TT group and 67.7% in the MenCCRM group with GMTs of 20.6 and 31.2.

- Percentages with hSBA-MenW-135 titres ≥1:8 were 83.1% in the ACWY-TT group and 43.3% in the MenCCRM group with GMTs of 59.3 and 9.2.

- Percentages with hSBA-MenY titres ≥1:8 were 88.8% in the ACWY-TT group and 71.0% in the MenCCRM group with GMTs of 117.9 and 35.7.

No SAEs considered to be possibly related to vaccination by the investigator or considered related to study participation were reported from the end of the 6-month Extended Safety Follow-up period following vaccination in study MENACWY-TT-081 until the Month 56 persistence time-point.

Ext 081 Month 68

All 241 subjects who returned for the M68 follow-up visit were offered a single dose of Nimenrix. The study report provides antibody persistence data at M68 and one month post-booster data at M69 for 220 subjects in the ATP cohort. In the ATP cohort for persistence at Month 68, the mean age at booster dose was 11.4 years with an equal gender split.

At Month 68 based on PHE rSBA data:

- Percentages with rSBA-MenA titres ≥1:8 were 86.5% in the ACWY-TT group and 29.5% in the MenCCRM group.
- Percentages with rSBA-MenC titres ≥1:8 were 39.9% in the ACWY-TT group and 62.3% in the MenCCRM group.
- Percentages with rSBA-MenW-135 titres ≥1:8 were 52.8% in the ACWY-TT group and 14.8% in the MenCCRM group.
- Percentages with rSBA-MenY titres ≥1:8 were 71.3% in the ACWY-TT group and 13.1% in the MenCCRM group.
- GMTs for the A, C, W-135, and Y serogroups were 129.5, 14.2, 59.2 and 139.4, respectively, in the ACWY-TT group compared to 11.1, 44.5, 7.8 and 6.8, respectively, in the MenCCRM group.

At one month post-booster vaccination (see below):

- All subjects from both initial vaccination groups had rSBA-MenA, rSBA-MenC, rSBA-MenW-135 rSBA-MenY titres ≥1:128.
- GMTs for the A, C, W-135 and Y serogroups were 5613.0, 5314.6, 14750.6 and 7954.6, respectively, in the ACWY-TT group compared to 3521.1, 7042.2, 10540.4 and 5829.2 in the MenCCRM group.

Synopsis Table 4: Number and percentage of subjects with rSBA-MenA (PHE), rSBA-MenC (PHE), rSBA-MenW-135 (PHE) and rSBA-MenY (PHE) titres equal to 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 (PHE)	ACWY-TT	PI(M68)	165	145	87.9	81.9	92.4	99	60.0	52.1	67.5	133.5	95.5	186.6
		PII(M69)	165	165	100	97.8	100	165	100	97.8	100	5613.0	4946.3	6369.4
	MenCCRM	PI(M68)	55	16	29.1	17.6	42.9	11	20.0	10.4	33.0	11.5	7.0	19.0
		PII(M69)	55	55	100	93.5	100	55	100	93.5	100	3521.1	2912.5	4256.9
rSBA-MenC (PHE)	ACWY-TT	PI(M68)	165	65	39.4	31.9	47.3	36	21.8	15.8	28.9	14.3	10.7	19.2
		PII(M69)	165	165	100	97.8	100	165	100	97.8	100	5314.6	4596.2	6145.4
	MenCCRM	PI(M68)	55	36	65.5	51.4	77.8	23	41.8	28.7	55.9	49.1	25.2	95.9
		PII(M69)	55	55	100	93.5	100	55	100	93.5	100	7042.2	5317.4	9326.5
rSBA-MenW-135 (PHE)	ACWY-TT	PI(M68)	165	87	52.7	44.8	60.5	77	46.7	38.9	54.6	57.1	37.5	87.1
		PII(M69)	165	165	100	97.8	100	165	100	97.8	100	14750.6	12779.6	17025.6
	MenCCRM	PI(M68)	55	8	14.5	6.5	26.7	7	12.7	5.3	24.5	7.9	4.9	12.7
		PII(M69)	55	55	100	93.5	100	55	100	93.5	100	10540.4	8455.2	13139.8
rSBA-MenY (PHE)	ACWY-TT	PI(M68)	165	115	69.7	62.1	76.6	106	64.2	56.4	71.5	123.8	83.8	182.8
		PII(M69)	165	165	100	97.8	100	165	100	97.8	100	7954.6	7167.8	8827.8
	MenCCRM	PI(M68)	55	6	10.9	4.1	22.2	5	9.1	3.0	20.0	6.5	4.3	9.9
		PII(M69)	55	55	100	93.5	100	55	100	93.5	100	5829.2	4725.6	7190.6

At Month 68 based on hSBA (GSK's assay) data in the M68 ATP cohort for immunogenicity:

- Percentages with hSBA-MenA titres ≥1:8 were 40.6% in the ACWYTT group and 35.6% in the MenCCRM group.
- Percentages with hSBA-MenC titres ≥1:8 were 75.6% in the ACWYTT group and 75.4% in the MenCCRM group.
- Percentages with hSBA-MenW-135 titres ≥1:8 were 78.6% in the ACWY-TT group and 36.5% in the MenCCRM group.

- Percentages with hSBA-MenY titres ≥1:8 were 73.0% in the ACWYTT group and 41.4% in the MenCCRM group.

- GMTs for A, C, W-135, and Y serogroups were 6.9, 28.4, 56.7 and 56.3 respectively, in the ACWY-TT group compared to 4.5, 34.3, 8.1 and 13.3 in the MenCCRM group.

At one month post booster vaccination (see below) in the Booster ATP cohort:

- All subjects in the ACWY-TT group had hSBA titres ≥1:8 for all 4 serogroups and at least 86.8% in the MenCCRM group had hSBA titres ≥1:8 against all 4 serogroups.

- GMTs for the A, C, W-135, and Y serogroups were 1376.5, 11986.8, 14582.1and 12835.9, respectively in the ACWY-TT group compared to 101.2, 13692.2, 235.7 and 527.3 in the MenCCRM group.

- Vaccine response rates for hSBA-MenA were 98.1% for ACWY-TT and 82.7% for MenCCRM.
- Vaccine response rates for hSBA-MenC were 98.1% for ACWY-TT and 92.0% for MenCCRM.
- Vaccine response rates for hSBA-MenW-135 were 97.8% for ACWY-TT and 75.6% for MenCCRM.
- Vaccine response rates for hSBA-MenY were 98.6% for ACWY-TT and 68.6% for MenCCRM.

Table 56 Number and percentage of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY titres 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-TT	PI(M68)	161	63	39.1	31.5	47.1	62	38.5	31.0	46.5	6.5	5.0	8.4
		PII(M69)	163	163	100	97.8	100	163	100	97.8	100	1376.5	1138.2	1664.6
	MenCCRM	PI(M68)	53	21	39.6	26.5	54.0	19	35.8	23.1	50.2	4.4	3.3	5.8
		PII(M69)	53	46	86.8	74.7	94.5	46	86.8	74.7	94.5	101.2	59.3	172.8
hSBA-MenC	ACWY-TT	PI(M68)	160	124	77.5	70.2	83.7	121	75.6	68.2	82.1	28.0	20.7	37.9
		PII(M69)	161	161	100	97.7	100	161	100	97.7	100	11986.8	10085.2	14247.0
	MenCCRM	PI(M68)	51	40	78.4	64.7	88.7	40	78.4	64.7	88.7	40.2	21.5	75.1
		PII(M69)	54	54	100	93.4	100	54	100	93.4	100	13692.2	10094.2	18572.8
hSBA-MenW-135	ACWY-TT	PI(M68)	147	114	77.6	69.9	84.0	114	77.6	69.9	84.0	54.8	39.5	76.1
		PII(M69)	156	156	100	97.7	100	156	100	97.7	100	14582.1	12448.5	17081.5
	MenCCRM	PI(M68)	46	17	37.0	23.2	52.5	17	37.0	23.2	52.5	8.1	4.6	14.3
		PII(M69)	52	50	96.2	86.8	99.5	50	96.2	86.8	99.5	235.7	152.0	365.5
hSBA-MenY	ACWY-TT	PI(M68)	147	106	72.1	64.1	79.2	106	72.1	64.1	79.2	53.8	37.2	77.9
		PII(M69)	160	160	100	97.7	100	160	100	97.7	100	12835.9	11074.4	14877.5
	MenCCRM	PI(M68)	52	21	40.4	27.0	54.9	21	40.4	27.0	54.9	13.2	6.7	26.3
		PII(M69)	54	52	96.3	87.3	99.5	52	96.3	87.3	99.5	527.3	356.5	779.9

The post-booster safety analysis was performed on the Booster TVC.

- During the 4-day post-boost period, at least one symptom (solicited or unsolicited) was reported by 71.5% in the ACWY-TT group and 77.4% in the MenCCRM group.

- Pain was the most frequently reported local symptom (66.1% in the ACWY-TT group and 58.3% in the MenCCRM group). Percentages with Grade 3 local symptoms ranged from 2.3% (swelling in the ACWY-TT group) to 6.7% (pain and redness in the MenCCRM group).

- Headache was the most frequently reported general symptom in the ACWY-TT group (25.4%) and fatigue was the most frequent in the MenCCRM group (20.7%). Grade 3 general symptoms were reported by a maximum of 4.1% (headache in ACWY-TT group). The percentage of reported general symptoms with a causal relationship to vaccination ranged from 5.2% to 17.2%. Grade 3

general symptoms with a causal relationship to vaccination were reported only in the ACWY-TT group, by a maximum of 3.0% of subjects.

- During the 31-day post-vaccination period, at least one unsolicited symptom was reported by 14.5% in the ACWY-TT group and 12.9% in the MenCCRM group. At least one grade 3unsolicited symptom was reported by 1.7% and 1.6% and at least one unsolicited symptom with causal relationship was reported by 3.4% vs. 1.6%. One in the ACWY-TT group reported grade 3 vomiting which was assessed by the investigator as causally related to vaccination.

- No SAEs were reported during the 31-day post-booster vaccination period.

Study 036/043 Adolescents vs. ACWY

The initial part of the study was conducted in 2007-8 in Asia. The target sample size was 1024 subjects who were randomised in a 3:1 ratio to the quadrivalent conjugate (N=768) and unconjugated (N=256) vaccines. Enrolment was stratified to ensure ~340 subjects in each of the three age strata of 11-13, 14-15 and 16-17 years. Of the 1025 subjects enrolled and vaccinated 1016 completed the study while 1012 were included in the ATP cohort for immunogenicity. The mean age was 14.3 years, 53% were female and the study population was of South, East and Southeast Asian heritage.

The applicant concluded that non-inferiority of ACWY-TT vs. Mencevax was demonstrated for each meningococcal group based on 95% CI around the differences in response rates within -1.8%.

Vaccine response rates one month after the vaccination (ATP cohort for immunogenicity)

		Group						Difference in response rate (ACWY-TT-MenPS)		
		ACWY-TT			MenPS				95% CI	
Antibody	Pre-vaccination status	N	n	%	N	n	%	%	LL	UL
rSBA-MenA	S-	103	103	100	46	46	100	0.00	-	-
	S+	512	422	82.4	169	125	74.0	8.46	-	-
	Total	615	525	**85.4***	215	171	79.5	5.83	**0.11**	12.28
rSBA-MenC	S-	291	288	99.0	98	98	100	-1.03	-	-
	S+	428	410	95.8	139	131	94.2	1.55	-	-
	Total	719	698	97.1	237	229	96.6	0.45	**-1.80**	3.75
rSBA-MenW-135	S-	135	135	100	45	45	100	0.00	-	-
	S+	582	557	95.7	197	168	85.3	10.43	-	-
	Total	717	692	**96.5***	242	213	88.0	8.50	**4.66**	13.35
rSBA-MenY	S-	67	67	100	36	36	100	0.00	-	-
	S+	670	619	92.4	210	156	74.3	18.10	-	-
	Total	737	686	**93.1***	246	192	78.0	15.03	**9.90**	20.87

Response rates to each meningococcal group were at or near 100% for both vaccines in subsets seronegative at baseline but were higher (only very slightly for MenC) with the conjugate in the subsets seropositive at baseline. The analyses were not performed separately for the three age strata.

Pre-vaccination percentages of subjects with rSBA titres ≥ 1:8 varied from 58.6%-59.4% for rSBA-MenC to 85.4%-90.9% for rSBA-MenY. One month after vaccination almost all subjects had titres ≥ 1:128 for the four serogroups. The rSBA GMTs for all serogroups increased in both vaccine groups by 16.4- to 274.3-fold following vaccination, with ranges of 44.5 to 368.2 pre-dose to 2679.3 to 13865.2 at one month post-dose. An exploratory analysis of the differences between the vaccine groups indicated that the rSBA GMTs adjusted for pre-vaccination measurements and age strata for all serogroups were significantly higher in the ACWY-TT group vs. the MenPS group.

Adjusted GMT ratios between groups one month post-dose (ATP cohort for immunogenicity)

	Group				Adjusted GMT ratio (ACWY-TT / MenPS)		
	ACWY-TT		MenPS			95% CI	
Antibody	N	Adjusted GMT	N	Adjusted GMT	Value	LL	UL
rSBA-MenA	615	6218.8	215	3362.0	1.85	1.62	2.11
rSBA-MenC	719	12889.7	237	8406.1	1.53	1.27	1.85
rSBA-MenW-135	717	8576.1	242	2735.9	3.13	2.72	3.62
rSBA-MenY	737	14020.1	246	5372.7	2.61	2.28	2.98

A subset of samples selected (using Gibb's method) from those of sufficient volume was also tested by rSBA at HPA and reported in the Y2 follow-up study report 043.

- At M24 the HPA data showed that rSBA titres ≥ 1:8 were observed in 74.3% (MenW) to 95.0% (MenC) from the ACWY-TT group compared to 26.1% (MenW) to 85.7% (MenA) from the *Mencevax* group. Percentages with rSBA-MenA titre ≥ 1:128, rSBA-MenC titre ≥ 1:8, rSBA-MenW-135 titre ≥ 1:8 and ≥ 1:128 and rSBA-MenY titre ≥ 1:8 and ≥ 1:128 were all statistically significantly higher for the ACWY-TT group. In addition, the rSBA GMTs were statistically significantly higher in the ACWY-TT for MenA, W and Y.
- At M24 the GSK rSBA data showed that all subjects had titres ≥ 1:8 for the four serogroups in the ACWY-TT group compared to 94-100% in the control group. The percentages with rSBA-MenA titre ≥ 1:128, rSBA-MenW-135 titre ≥ 1:8 and ≥ 1:128 and rSBA-MenY titre ≥ 1:8 and ≥ 1:128 were all statistically significantly higher for the ACWY-TT group. In addition, the GMTs were statistically significantly higher in the ACWY-TT for MenA, W and Y.

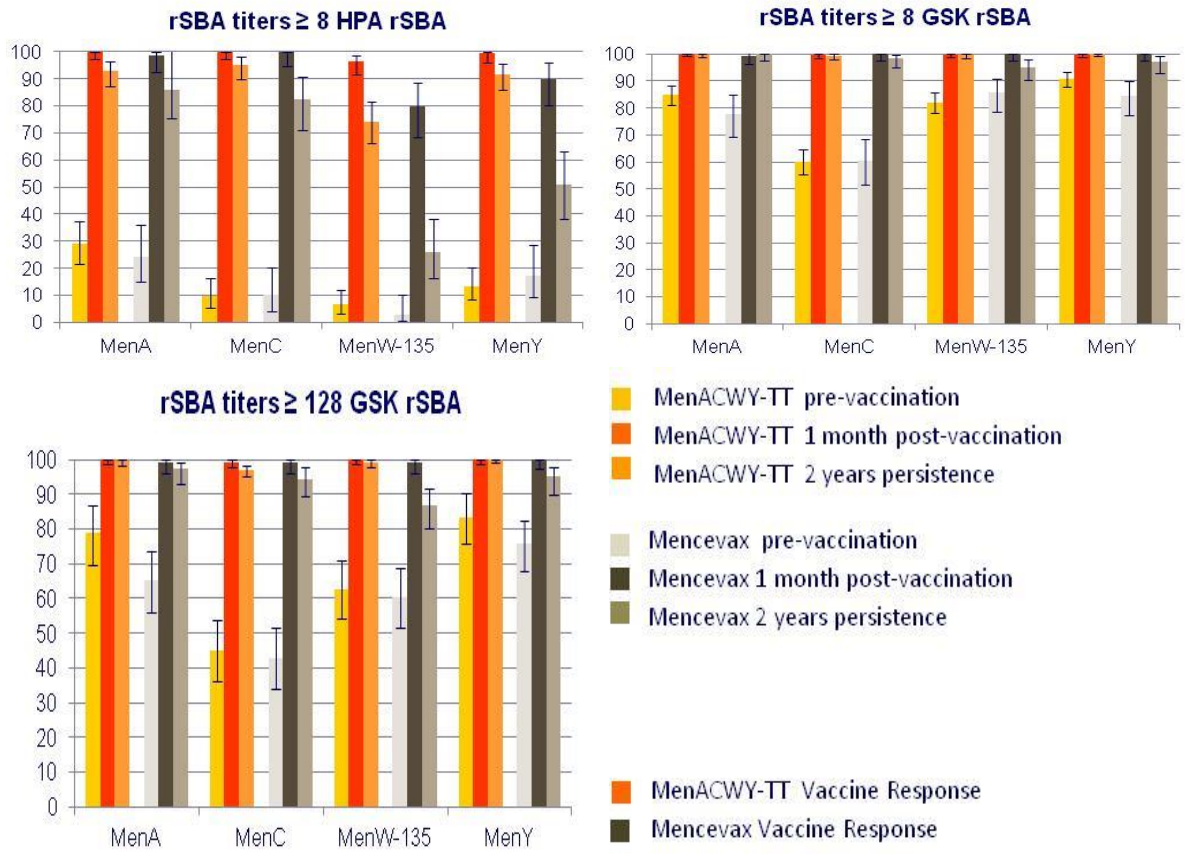
The table below shows the HPA data from M0, M1 and M24. In particular, note that much lower percentages were reported as being seropositive at baseline using the HPA rSBA assay.

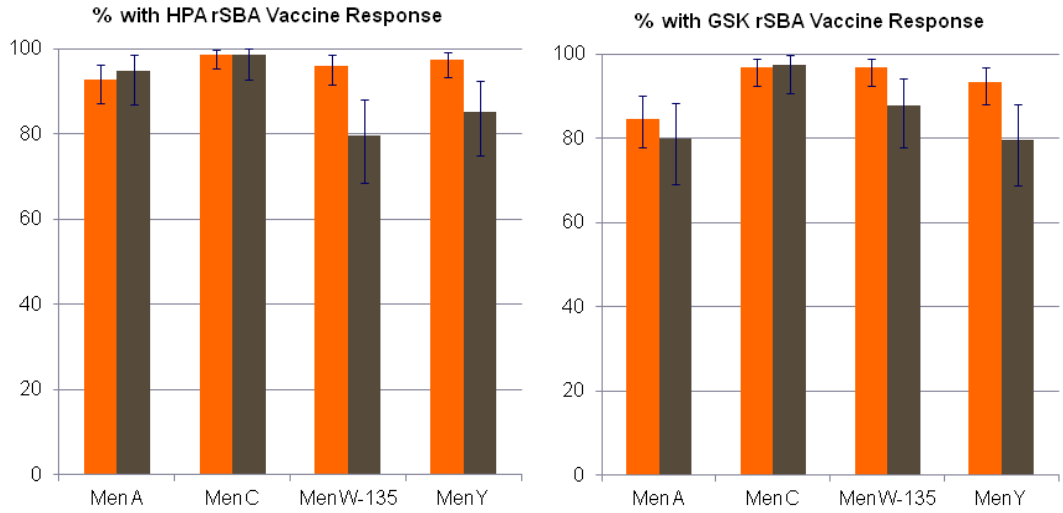
rSBA titres and GMTs (ATP cohort for persistence at Month 24, SELHPA)

				≥ 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	PRE	138	40	29.0	21.6	37.3	30	21.7	15.2	29.6	8.7	5.8	13.1
		PI(M1)	138	138	100	97.4	100	137	99.3	96.0	100	3015.1	2507.4	3625.4
		PI(M24)	138	128	92.8	87.1	96.5	125	90.6	84.4	94.9	463.1	338.8	633.0
	MenPS	PRE	70	17	24.3	14.8	36.0	13	18.6	10.3	29.7	7.2	4.1	12.8
		PI(M1)	70	69	98.6	92.3	100	68	97.1	90.1	99.7	1598.9	1110.2	2302.7
		PI(M24)	70	60	85.7	75.3	92.9	56	80.0	68.7	88.6	207.9	121.4	356.1
rSBA-MenC	ACWY-TT	PRE	141	14	9.9	5.5	16.1	9	6.4	3.0	11.8	3.1	2.5	3.9
		PI(M1)	141	141	100	97.4	100	141	100	97.4	100	4016.2	3311.0	4871.7
		PI(M24)	141	134	95.0	90.0	98.0	124	87.9	81.4	92.8	368.3	279.6	485.3
	MenPS	PRE	68	7	10.3	4.2	20.1	2	2.9	0.4	10.2	2.9	2.2	3.7
		PI(M1)	68	68	100	94.7	100	67	98.5	92.1	100	2435.5	1721.3	3446.1
		PI(M24)	68	56	82.4	71.2	90.5	54	79.4	67.9	88.3	280.6	150.4	523.5
rSBA-MenW-135	ACWY-TT	PRE	139	9	6.5	3.0	11.9	8	5.8	2.5	11.0	2.7	2.2	3.4
		PI(M1)	139	134	96.4	91.8	98.8	134	96.4	91.8	98.8	2903.5	2135.2	3948.4
		PI(M24)	136	101	74.3	66.1	81.4	89	65.4	56.8	73.4	112.1	71.6	175.5
	MenPS	PRE	69	2	2.9	0.4	10.1	2	2.9	0.4	10.1	2.4	1.9	3.0
		PI(M1)	69	55	79.7	68.3	88.4	55	79.7	68.3	88.4	319.3	163.3	624.4
		PI(M24)	69	18	26.1	16.3	38.1	12	17.4	9.3	28.4	7.0	4.1	11.9
rSBA-MenY	ACWY-TT	PRE	142	19	13.4	8.3	20.1	16	11.3	6.6	17.7	3.8	2.9	5.0
		PI(M1)	142	141	99.3	96.1	100	141	99.3	96.1	100	3240.4	2687.1	3907.6
		PI(M24)	142	130	91.5	85.7	95.6	123	86.6	79.9	91.7	462.1	333.0	641.4
	MenPS	PRE	69	12	17.4	9.3	28.4	11	15.9	8.2	26.7	4.7	3.0	7.5
		PI(M1)	69	62	89.9	80.2	95.8	60	87.0	76.7	93.9	527.7	315.5	882.6
		PI(M24)	69	35	50.7	38.4	63.0	30	43.5	31.6	56.0	26.2	13.7	50.1

The first three figures below show the percentages of subjects with HPA and GSK rSBA titres ≥ 8 and GSK rSBA titres ≥ 128 at M0, M1 and M24 and the percentages with a vaccine response at M1 using each assay. The GSK rSBA assay resulted in generally higher titres than the HPA assay especially noticeable at M0. The HPA rSBA assay better discriminated between ACWY-TT and *Mencevax*, especially at the 2-year persistence time point, and gave results in favour of the conjugate vaccine.

The last two figures compare the response rates at M1 using each assay. Whichever assay is applied the results suggest that vaccine response rates were at least as good with the conjugate vaccine vs. the control vaccine.





In both vaccine groups, anti-PS GMCs for all serogroups reached values within the range 14.81 to 86.63 μg/mL compared to pre-vaccination values from 0.19 to 1.06 μg/mL. Pre-vaccination percentages with anti-PS concentrations ≥ 0.3 μg/mL varied from 9.8%-12.4% for anti-PSW-135 to 70.1%-74.0% for anti-PSA. One month post-vaccination the percentages with ≥ 0.3 μg/mL increased to 98.7%-100.0% across the two vaccine groups while ≥ 2.0 μg/mL was achieved in 97.6%-100.0% for groups A, C and Y and 93.7%-94.8% for group W-135. Exploratory evaluation of the between-group differences indicated statistically significantly higher anti-PSA GMCs and lower anti-PSC GMCs (adjusted for pre-vaccination measurements and age strata) in the ACWY-TT group compared to the MenPS group.

The percentages with pre-vaccination anti-TT antibody concentration ≥ 0.1 IU/mL were 67.4% and 72.2% in the ACWY-TT and the MenPS groups, respectively. One month post-vaccination the anti-TT GMC had increased by 26.2-fold and the percentage with ≥ 0.1 IU/mL had increased to 97.8% in the ACWY-TT group. Both values remained essentially unchanged in the MenPS group. Exploratory evaluation of the between-group differences indicated a statistically significantly higher proportion with anti-TT ≥ 0.1 IU/mL and GMC adjusted for pre-vaccination measurements and age strata in the ACWY-TT group compared to the MenPS group.

Month 60

The Month 60 (Y5) persistence study was conducted by three principal investigators at three centres in two countries (two in India and one in the Philippines).

The rSBA testing at Months 36, 48 and 60 was done at the PHE (formerly HPA; see primary results above) laboratory in the United Kingdom. The results using the PHE assay have been shown for each time point in the table below. However, it should be noted that only a small subset had sera tested using this assay before M36. No hSBA data are reported from the later follow-up time points.

Of the 790 subjects enrolled in India and the Philippines in the initial study (036) 478 participated in the Month 60 persistence visit but 155/478 (119 ACWY-TT and 36 MenPS) were not compliant with the blood sampling schedule and one other had essential serological data missing. The ATP cohort for persistence at Month 60 comprised 322 subjects.

At M60 the percentages of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres ≥ 1:8 were 97.5%, 88.6%, 86.0% and 96.6% in the ACWY-TT group and 93.0%, 87.1%, 34.9%

and 66.3% in the MenPS group, respectively. The GMTs were higher for ACWY-TT except that the MenC GMTs were comparable between the two vaccine groups.

Number and percentage of subjects with rSBA-MenA (PHE), rSBA-MenC (PHE), rSBA-MenW-135 (PHE), and rSBA-MenY (PHE) titres equal to or above the cut-off values of 1:8 and 1:128 and GMTs from Month 0 to Month 60 (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	PRE	60	19	31.7	20.3	45.0	14	23.3	13.4	36.0	16.0	9.1	28.1
		PI(M1)	60	60	100	94.0	100	60	100	94.0	100	3404.8	2535.9	4571.3
		PI(M24)	60	55	91.7	81.6	97.2	53	88.3	77.4	95.2	494.6	305.9	799.6
		PI(M36)	236	222	94.1	90.2	96.7	211	89.4	84.8	93.0	487.1	391.0	606.7
		PI(M48)	234	206	88.0	83.2	91.9	198	84.6	79.3	89.0	333.2	259.4	428.0
		PI(M60)	236	230	97.5	94.5	99.1	219	92.8	88.7	95.7	643.8	530.7	781.0
	MenPS	PRE	33	9	27.3	13.3	45.5	6	18.2	7.0	35.5	11.4	5.7	22.9
		PI(M1)	33	32	97.0	84.2	99.9	31	93.9	79.8	99.3	1403.2	732.2	2689.4
		PI(M24)	33	27	81.8	64.5	93.0	25	75.8	57.7	88.9	199.0	87.3	453.5
		PI(M36)	86	72	83.7	74.2	90.8	66	76.7	66.4	85.2	185.4	120.1	286.3
		PI(M48)	86	67	77.9	67.7	86.1	62	72.1	61.4	81.2	139.9	88.2	221.9
		PI(M60)	86	80	93.0	85.4	97.4	71	82.6	72.9	89.9	296.0	202.4	432.9
rSBA-MenC	ACWY-TT	PRE	63	8	12.7	5.6	23.5	7	11.1	4.6	21.6	6.7	4.6	9.8
		PI(M1)	63	63	100	94.3	100	63	100	94.3	100	3919.6	2883.5	5328.1
		PI(M24)	63	58	92.1	82.4	97.4	56	88.9	78.4	95.4	337.1	219.6	517.2
		PI(M36)	236	210	89.0	84.3	92.7	196	83.1	77.6	87.6	339.4	260.6	442.0
		PI(M48)	233	216	92.7	88.6	95.7	202	86.7	81.6	90.8	325.8	258.8	410.0
		PI(M60)	236	209	88.6	83.8	92.3	188	79.7	74.0	84.6	248.6	194.2	318.2
	MenPS	PRE	41	4	9.8	2.7	23.1	3	7.3	1.5	19.9	5.9	3.9	8.9
		PI(M1)	41	41	100	91.4	100	41	100	91.4	100	2970.7	2014.1	4381.5
		PI(M24)	41	36	87.8	73.8	95.9	35	85.4	70.8	94.4	425.1	220.1	821.0
		PI(M36)	86	73	84.9	75.5	91.7	63	73.3	62.6	82.2	405.3	229.5	715.8
		PI(M48)	86	76	88.4	79.7	94.3	70	81.4	71.6	89.0	405.3	245.2	669.8
		PI(M60)	85	74	87.1	78.0	93.4	68	80.0	69.9	87.9	366.5	224.1	599.4

				≥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-MenW-135	ACWY-TT	PRE	73	5	6.8	2.3	15.3	5	6.8	2.3	15.3	5.3	4.1	6.8
		PI(M1)	73	71	97.3	90.5	99.7	71	97.3	90.5	99.7	3051.6	2090.5	4454.4
		PI(M24)	72	56	77.8	66.4	86.7	51	70.8	58.9	81.0	179.3	103.8	309.5
		PI(M36)	236	193	81.8	76.3	86.5	187	79.2	73.5	84.2	326.7	239.6	445.3
		PI(M48)	233	188	80.7	75.0	85.6	179	76.8	70.9	82.1	248.5	183.4	336.7
		PI(M60)	236	203	86.0	80.9	90.2	195	82.6	77.2	87.2	436.9	324.4	588.4
	MenPS	PRE	32	2	6.3	0.8	20.8	2	6.3	0.8	20.8	5.4	3.5	8.3
		PI(M1)	32	25	78.1	60.0	90.7	25	78.1	60.0	90.7	291.5	114.8	740.1
		PI(M24)	32	9	28.1	13.7	46.7	5	15.6	5.3	32.8	11.6	5.8	23.1
		PI(M36)	86	25	29.1	19.8	39.9	19	22.1	13.9	32.3	13.2	8.4	20.7
		PI(M48)	86	25	29.1	19.8	39.9	17	19.8	12.0	29.8	12.4	7.9	19.4
		PI(M60)	86	30	34.9	24.9	45.9	26	30.2	20.8	41.1	19.7	11.8	32.9

rSBA-MenY	ACWY-TT	PRE	69	7	10.1	4.2	19.8	6	8.7	3.3	18.0	6.3	4.5	8.9
		PI(M1)	69	68	98.6	92.2	100	68	98.6	92.2	100	2824.5	2118.1	3766.5
		PI(M24)	69	60	87.0	76.7	93.9	58	84.1	73.3	91.8	386.5	234.6	636.5
		PI(M36)	236	220	93.2	89.2	96.1	212	89.8	85.2	93.4	779.2	609.9	995.7
		PI(M48)	232	212	91.4	87.0	94.7	204	87.9	83.0	91.8	713.3	542.9	937.3
		PI(M60)	236	228	96.6	93.4	98.5	225	95.3	91.8	97.7	1000.2	824.1	1214.0
	MenPS	PRE	33	9	27.3	13.3	45.5	8	24.2	11.1	42.3	12.4	6.3	24.6
		PI(M1)	33	30	90.9	75.7	98.1	29	87.9	71.8	96.6	593.1	298.6	1178.1
		PI(M24)	33	18	54.5	36.4	71.9	14	42.4	25.5	60.8	38.7	17.0	88.0
		PI(M36)	86	54	62.8	51.7	73.0	47	54.7	43.5	65.4	83.5	46.3	150.7
		PI(M48)	86	45	52.3	41.3	63.2	43	50.0	39.0	61.0	67.7	36.0	127.3
		PI(M60)	86	57	66.3	55.3	76.1	56	65.1	54.1	75.1	124.9	71.2	219.3

There were some baseline differences between India and Philippine adolescents with higher baseline seropositivity rates in India for MenA and to a lesser extent for MenC. At M60 the GMTs for Men A, W135 and Y (but not Men C) were significantly higher in both Indian subjects and Philippine subjects who had received the conjugate vaccine vs. the unconjugated vaccine subsets.

The MenA GMTs were significantly higher for Indian vs. Philippine subjects in both vaccine groups. The MenC GMT was significantly higher in Philippine subjects vs. Indian subjects who had each received the conjugate vaccine but there was no difference among those who received unconjugated polysaccharide. For MenC the GMT was numerically higher for plain polysaccharide among Indian subjects but there was no difference between vaccine groups among Philippine subjects. The MenY GMT was significantly higher in Indian vs. Philippine subjects who had each received the conjugate vaccine but there was no difference among those who received unconjugated polysaccharide.

No SAEs that were related to study procedures or concurrent GSK medication were reported from the last visit of the primary vaccination study (MENACWY-TT-036) up to 60 months after primary vaccination.

2.3.3. Discussion on clinical aspects

Study 081/088 M56, M68 and response to a booster dose in children aged 2-10 years

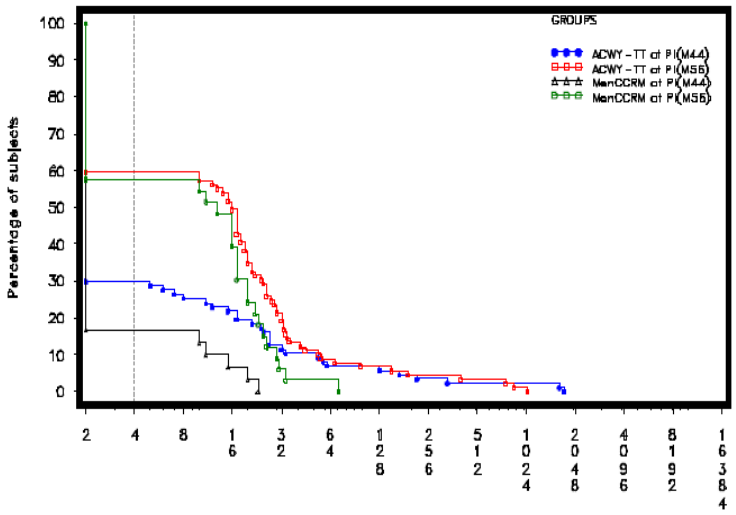
In the original study rSBA was assayed at GSK's laboratories and non-inferiority of ACWY-TT vs. *Menjugate* was demonstrated for responses to MenC with numerically comparable findings within subsets according to baseline MenC serostatus. The supplementary tables of the response rates by age strata showed that responses to the MenC conjugates were comparable and responses to MenA, W and Y were all much higher in the ACWY-TT group regardless of baseline serostatus. GMTs tended to be lower in the younger subjects compared to the older subjects. In each age stratum the rSBA GMT for MenC was lower with ACWY-TT than with Menjugate (ratios 0.43 and 0.57).

At Month 56 based on PHE rSBA data there were clear differences between ACWY-TT and Menjugate groups for seropositivity to MenA, W135 and Y reflecting the immune responses to the additional conjugates in Nimenrix. For MenC the percentages with rSBA-MenC titres ☐1:8 (59.1% vs. 64.6%) and with ☐1:128 (34.9% vs. 49.2%) as well as the GMT were numerically lower in the ACWY-TT group.

At Month 56 based on GSK's hSBA assay the MenC antibody levels supported a conclusion of broad comparability as deduced from the rSBA data. The MenW135 and MenY data did suggest a benefit for prior vaccination with Nimenrix but the difference was not so marked, especially for MenY. The MenA

data are a surprise not only because the seropositivity rates and GMTs were comparable but also because these rates seemingly increased between M32 and M44 (<30% and < 20% for respective vaccine groups) compared to M56 (near to 60%). However, the GMTs remained low, suggesting that many subjects must have had titres near to 1:4 and 1:8, which is borne out by the RCD shown below.

Figure 5 **Reverse cumulative distribution curves for hSBA-MenA titres at Month 44 and Month 56 follow-up (ATP cohort for persistence at Month 56)**



On this basis it remains possible that a small change in assay conditions, including use of a different pool of human complement, may have influenced the results. No assay details are provided to substantiate this hypothesis but these should be provided when the planned variation is filed.

At Month 68 based on PHE rSBA data the pattern was similar to that at M56 except that there seemed to be an advantage for MenC rSBA in the Menjugate group with non-overlapping 95% CI for percentages at ≥1:8 and ≥1:128 as well as the GMTs. Nevertheless, with a much smaller Menjugate group a few outliers could have influenced the overall results, which need to be viewed with some caution.

The PHE rSBA data clearly showed that a dose of Nimenrix was able to boost the MenC responses in subjects primed with the same vaccine and in those primed with the CRM197 conjugate. The data also showed that the GMTs to MenA, W135 and Y were all higher in primed vs. previously unvaccinated subjects, supporting the conclusion that the first dose of Nimenrix successfully primed subjects against the other serogroups.

At Month 68 the hSBA (GSK's assay) data indicated that the titres against MenA had fallen in both vaccine groups since the unexpected findings at M56. This again suggests a problem with the assay rather than a real phenomenon. Apart from the MenC titres in both groups and the MenW135 titres in the ACWY-TT group the other titres also showed a decline from the previous time point.

At one month post booster vaccination the hSBA results supported the ability of Nimenrix to prime subjects against all four serogroups and to boost MenC responses regardless of the type of conjugate used for priming. A single dose of Nimenrix also elicited good primary responses to MenA, W135 and Y in the Menjugate group although the immune response was much weaker against MenA than against MenW135 and MenY.

The follow-up and post-booster safety analyses from this study do not raise any new concerns.

Study 036/043 Adolescents vs. ACWY up to M60

In Asian adolescents who received either Nimenrix or unconjugated MenACWY, the initial study suggested a small degree of benefit for the conjugate. In addition to this, all other evidence pointed to a benefit for the conjugate in terms of priming, which does not occur with unconjugated polysaccharides. Based on the GSK rSBA assay the GMTs were all much higher with the conjugated vaccine. The HPA/PHE rSBA assay results supported the conclusions from the GSK assay up to M24 even though much lower percentages were reported as being seropositive at baseline using the HPA rSBA assay and the GMTs were lower. Based on a randomly selected subset, the HPA rSBA assay better discriminated between ACWY-TT and *Mencevax*, especially at the 2-year persistence time point, and gave results in favour of the conjugate vaccine.

The Month 60 (Y5) persistence study must be viewed in light of the fact that it was conducted at only three of the original study centres and only in two countries. Also, only rSBA results using the PHE assay are available from M36 onwards. These data suggest high persistent seropositivity rates at M60 and higher rates with the conjugate for rSBA-MenW-135 and rSBA-MenY. In addition GMTs were higher for ACWY-TT except that the MenC GMTs were comparable between the two vaccine groups.

There were some baseline differences between India and Philippine adolescents with higher baseline seropositivity rates in India for MenA and to a lesser extent for MenC. At M60 the GMTs for Men A, W135 and Y (but not Men C) were significantly higher in Indian subjects and in Philippine subjects who had received the conjugate vaccine vs. unconjugated vaccine.

The MenA GMTs were significantly higher for Indian vs. Philippine subjects in both vaccine groups. The MenC GMT was significantly higher in Philippine subjects vs. Indian subjects who had each received the conjugate vaccine but there was no difference among those who received unconjugated polysaccharide. For MenC the GMT was numerically higher for plain polysaccharide among Indian subjects but there was no difference between vaccine groups among Philippine subjects. The MenY GMT was significantly higher in Indian vs. Philippine subjects who had each received the conjugate vaccine but there was no difference among those who received unconjugated polysaccharide.

In conclusion

The available follow-up data from both studies raise no new concerns and the pre/post boost data indicate that Nimenrix effectively primes children and is able to boost MenC responses following priming with an alternative conjugate. The rSBA assays and hSBA assay (the latter being GSK's in-house assay) generally paint a similar picture even though the results are numerically quite different.

There are some issues that do need to be addressed, such as presenting the data from the extension of study 081 by age sub-group and discussing the rather strange pattern of MenA findings over time. However, these issues can be taken up within the forthcoming variation planned to be filed in December 2015. On that basis the assessor proposes not to issue a RSI at this time but to address all issues under that single variation intended to update the information in the current SmPC.

3. Rapporteur's overall conclusion and recommendation

☒ **Fulfilled:**

No further action required, however further data are expected in the context of a variation which the MAH has stated will be filed in December 2015. This variation will also include some of the other data assessed thus far under P046.

4. Additional clarification requested

N/A