EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Nimenrix

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

Procedure No. EMEA/H/C/002226/P46/0020

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.

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.

The MAH submitted the synoptic report for the paediatric study MenACWY-TT-088 EXT081 Month 44 in accordance with Article 46 of Regulation (EC) No 1901/2006.

The MAH has stated that, in accordance with Article 16(2) of Regulation (EC) No 726/2004, the data submitted do not influence the benefit-risk balance for Nimenrix. No urgent action is required regarding the SmPC. However, the MAH has planned to file a variation during 2013 in which data collected from a range of studies already submitted under Article 46 will be resubmitted to support changes to section 5.1 of the SmPC (i.e. to add antibody persistence data).

2. Recommendation

No SmPC and PL changes are proposed. The assessor agrees that a single variation may be filed to add information derived from several antibody persistence studies.

3. Introduction

MenACWY-TT-088 EXT081 M44 represents the follow-up to Year 4 of subjects who were initially enrolled into the primary study MenACWY-TT-081.

The primary phase data from study MenACWY-TT-081 were submitted as part of the initial MAA for Nimenrix.

Further follow-up of the subjects is planned up to 68 months after primary vaccination in MenACWY-TT-081.

4. Scientific Discussion

In the initial application dossier the data were presented as follows:

Study	Population	Study groups
MenACWY-TT-081 (Germany, France)	**Children** 2-10 years of age	**MenACWY-TT** Menjugate

In the initial study 081

The target sample size was 400 subjects who were to be randomised in a 3:1 ratio to ACWY-TT or *Menjugate*. Enrolment was stratified to provide approximately 200 subjects in each of the two age

strata of 2-5 and 6-10 years. The applicant concluded that this sample would provide power to meet the non-inferiority immunogenicity criterion of at least 85.6%.

The study was conducted in 2008-9. All of the 414 subjects enrolled and vaccinated completed the initial phase and 310 completed the longer-term follow-up while 296 were included in the ATP-I cohort. 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.

The applicant concluded that 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 comparable 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.

Month 44 data from 088

Of the 414 subjects enrolled in the initial study 081 there were 261 subjects who were followed up at the Month 44 persistence time-point, as shown below.

Synopsis Table 1: Study Population (Total cohort at Month 44)		
Number of subjects	**ACWY-TT**	**MenCCRM**
Planned, N	135	45
Enrolled in study 088, N (Total Cohort at Month 44)	193	68
Completed Month 44, n (%)	193 (100)	68 (100)
Demographics	**ACWY-TT**	**MenCCRM**
N (Total Cohort at Month 44)	193	68
Females:Males	96:97	31:37
Mean Age, years (SD)	9.3 (2.55)	9.1 (2.40)
White - Caucasian / European heritage, n (%)	165 (85.5)	58 (85.3)
ACWY-TT = Primed with MenACWY-TT in the primary vaccination study MENACWY-TT-081 PRI (111414) MenCCRM = Primed with *Menjugate* in the primary vaccination study MENACWY-TT-081 PRI (111414) N = total number of subjects n (%) = number / percentage of subjects in a given category		

The rSBA serological testing at pre-vaccination and one month post-vaccination in 081 were performed at GSK laboratories but the Month 32 and Month 44 samples were tested only at the Health Protection Agency (HPA) laboratories in the United Kingdom. For this reason, the M32 and M44 data have been presented in separate tables and the antibody kinetics and decay in plasma antibody levels between 081 and 088 cannot be directly assessed.

At Month 44 after primary vaccination the HPA rSBA data showed the following:

- The percentages with rSBA-MenA titres ≥1:8 were 85.7% in the ACWY-TT group and 25.8% in the MenCCRM group.
- The percentage with rSBA-MenC titres ≥1:8 were 37.0% in the ACWY-TT group and 45.5% in the MenCCRM group.
- The percentage with rSBA-MenW-135 titres ≥1:8 were 68.3% in the ACWY-TT group and 10.6% in the MenCCRM group.
- The percentage of subjects with rSBA-MenY titres ≥1:8 were 62.4% in the ACWY-TT group and 6.1% in the MenCCRM group.

Table 9 **Percentage of subjects with HPA rSBA titres equal to or above the cut-off values of 1:8 and 1:128 and GMTs at Month 32 and Month 44 follow-up (ATP cohort for persistence at Month 44)**

				≥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)	183	160	87.4	81.7	91.9	134	73.2	66.2	79.5	205.5	149.9	281.7
		PI(M44)	189	162	85.7	79.9	90.4	151	79.9	73.5	85.4	307.5	223.7	422.8
	MenCCRM	PI(M32)	66	15	22.7	13.3	34.7	9	13.6	6.4	24.3	8.3	5.6	12.3
		PI(M44)	66	17	25.8	15.8	38.0	16	24.2	14.5	36.4	13.5	8.0	23.0
rSBA-MenC	ACWY-TT	PI(M32)	182	115	63.2	55.7	70.2	65	35.7	28.8	43.1	32.7	24.4	44.0
		PI(M44)	189	70	37.0	30.1	44.3	38	20.1	14.6	26.5	14.5	10.9	19.2
	MenCCRM	PI(M32)	66	50	75.8	63.6	85.5	34	51.5	38.9	64.0	88.6	47.4	165.7
		PI(M44)	66	30	45.5	33.1	58.2	23	34.8	23.5	47.6	31.0	16.6	58.0
rSBA-MenW-135	ACWY-TT	PI(M32)	183	141	77.0	70.3	82.9	129	70.5	63.3	77.0	213.4	147.5	308.9
		PI(M44)	189	129	68.3	61.1	74.8	120	63.5	56.2	70.4	103.5	72.5	147.6
	MenCCRM	PI(M32)	66	5	7.6	2.5	16.8	5	7.6	2.5	16.8	5.7	4.2	7.8
		PI(M44)	66	7	10.6	4.4	20.6	5	7.6	2.5	16.8	5.9	4.3	8.1
rSBA-MenY	ACWY-TT	PI(M32)	183	149	81.4	75.0	86.8	138	75.4	68.5	81.5	227.6	163.6	316.7
		PI(M44)	189	118	62.4	55.1	69.4	107	56.6	49.2	63.8	78.9	54.6	114.0
	MenCCRM	PI(M32)	66	10	15.2	7.5	26.1	8	12.1	5.4	22.5	7.4	5.1	10.9
		PI(M44)	66	4	6.1	1.7	14.8	3	4.5	0.9	12.7	4.9	3.9	6.2

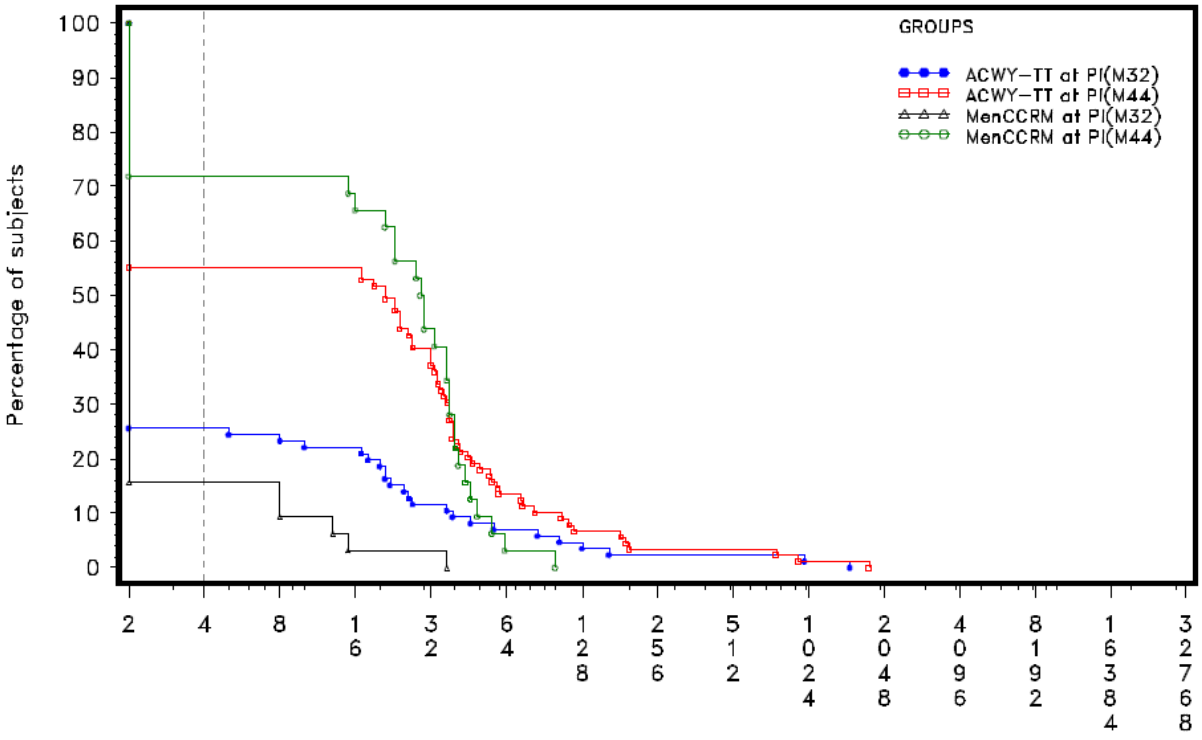
In contrast to the rSBA data, the hSBA data showed much lower antibody persistence against MenA (see initial assessment reports on this recognised discrepancy between the assays) but suggested better antibody persistence against the other meningococcal groups than indicated by the rSBA titres. Another anomaly of these data is the fact that in both vaccine groups the hSBA titres against MenA increased between M32 and M44 since no marked natural boosting effect would be expected.

Table 10 **Percentage of subjects with hSBA titres equal to or above the cut-off values of 1:4 and 1:8 and GMTs at Month 32 and Month 44 follow-up (ATP cohort for persistence at Month 44)**

				≥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)	86	22	25.6	16.8	36.1	21	24.4	15.8	34.9	4.3	3.2	6.0
		PI(M44)	89	49	55.1	44.1	65.6	49	55.1	44.1	65.6	12.0	8.2	17.4
	MenCCRM	PI(M32)	32	5	15.6	5.3	32.8	5	15.6	5.3	32.8	2.7	2.1	3.5
		PI(M44)	32	23	71.9	53.3	86.3	23	71.9	53.3	86.3	15.6	9.6	25.4
hSBA-MenC	ACWY-TT	PI(M32)	86	82	95.3	88.5	98.7	82	95.3	88.5	98.7	73.4	51.4	104.9
		PI(M44)	82	63	76.8	66.2	85.4	63	76.8	66.2	85.4	36.4	23.1	57.2
	MenCCRM	PI(M32)	31	28	90.3	74.2	98.0	28	90.3	74.2	98.0	90.4	36.2	225.6
		PI(M44)	31	20	64.5	45.4	80.8	20	64.5	45.4	80.8	38.8	13.3	113.2
hSBA-MenW-135	ACWY-TT	PI(M32)	81	68	84.0	74.1	91.2	68	84.0	74.1	91.2	66.8	45.1	98.9
		PI(M44)	87	70	80.5	70.6	88.2	70	80.5	70.6	88.2	64.3	42.7	96.8
	MenCCRM	PI(M32)	22	4	18.2	5.2	40.3	4	18.2	5.2	40.3	3.9	2.0	7.5
		PI(M44)	30	8	26.7	12.3	45.9	8	26.7	12.3	45.9	5.2	2.8	9.5
hSBA-MenY	ACWY-TT	PI(M32)	86	69	80.2	70.2	88.0	69	80.2	70.2	88.0	75.5	49.0	116.1
		PI(M44)	76	63	82.9	72.5	90.6	63	82.9	72.5	90.6	126.7	78.0	205.7
	MenCCRM	PI(M32)	27	13	48.1	28.7	68.1	13	48.1	28.7	68.1	16.3	6.6	40.2
		PI(M44)	26	12	46.2	26.6	66.6	12	46.2	26.6	66.6	16.8	6.3	44.9

This unexpected finding and the fact that the M44 titres are actually higher in the control group are shown in the RCD below.

Figure 5 **Reverse cumulative curves for hSBA-MenA antibody titres at Month 32 and Month 44 follow-up (ATP cohort for persistence at Month 44)**



No SAEs or deaths related to study participation or related to concurrent GSK drug and/or vaccine were reported from the end of the six-month Extended Safety Follow-up period following vaccination in study 081 until the Month 44 persistence time-point.

5. Rapporteur's Overall Conclusion and Recommendation

Overall conclusion

Based on the HPA rSBA data, the M44 data indicate that > 60% of subjects who had received MenACWY-TT in study 081 retained at least rSBA titres 1:8 except for MenC, for which the rates were 37% in the Nimenrix group and 45% in the Menjugate group. The highest persistence was observed against MenA.

In this regard the hSBA not only show the expected anomaly vs. rSBA regarding persistence of anti-MenA antibody but also show unexpected marked increments between M32 and M44 in both vaccine groups. This is a very strange finding for which there is no immediately obvious explanation for children resident within the EU. However, this is an issue that the MAH can address during the forthcoming variation.

It is not possible to draw any conclusions regarding the need for booster doses from these data.

Recommendation

The data should be added to the SmPC as already planned by the MAH in a forthcoming variation procedure.