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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/P46/0018

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 report for the paediatric study MenACWY-TT-019 EXT015 Year 4 in accordance with Article 46 of Regulation (EC) No 1901/2006. A short critical expert overview was also provided.

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-019 EXT015 Y4 represents the follow-up to Year 4 of subjects who were initially enrolled into the primary study MenACWY-TT-015.

The primary phase study MenACWY-TT-015, as well as the follow-up studies after 1 and 2 years (MenACWY-TT-016 and 017 respectively) were submitted as part of the initial MAA for Nimenrix.

The Year 3 follow-up data in study MenACWY-TT-018 were submitted under Article 46 in July 2012 (Art 46 reference P46-008).

Further follow-up of the subjects is planned up to 10 years after primary vaccination in MenACWY-TT-015.

4. Scientific Discussion

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

Study	Population	Study groups
MenACWY-TT-015/016/017 (Philippines, Saudi Arabia) 016 + 017 Persistence at 12 and 24 months	**Adolescents** **Adults** Stratified: • 11 to 17 years • 18-55 years	**MenACWY-TT** Mencevax ACWY

In the initial study 015

The target sample size was 500 enrolled subjects who were randomised in a 3:1 ratio to the quadrivalent conjugate (N=375) and unconjugated (N=125) vaccines. Enrolment was stratified to ensure 300 subjects in the 11-17 years and 200 in the 18-55 years age stratum. The applicant concluded that this sample would provide power to meet the immunogenicity criterion of at least 90% and power to meet the safety criterion of at least 86%. The initial study was conducted in 2006-8 and planned to continue to Year 5.

Of the 500 subjects enrolled and vaccinated 497 (372 and 125 per group) completed the initial study while 455 subjects (341 and 114) were included in the ATP-I cohort. The mean age at baseline was 18.3 years (SD 8 years), 49.5% were female, 66% were 11 to 17 years of age and the population was predominantly of Asian - South East Asian heritage (87.3%).

From study 015 the applicant concluded that non-inferiority of the conjugate vs. *Mencevax* was demonstrated for each of the four meningococcal groups based on 95% CI around the differences in vaccine *response rates* that were within -4%. A vaccine response was defined as:

- For initially seronegative subjects, post vaccination rSBA titre ≥ 1:32

- For initially seropositive subjects, a ≥4-fold increase in rSBA titre from pre to post vaccination.

Response rates to each meningococcal group in the subsets seropositive at baseline were numerically higher with the conjugate vaccine. Similar analyses applied to the TVC also demonstrated that the non-inferiority criterion was met with 95% CIs that were within -5.2% and a similar pattern of response rates as noted in the ATP cohort.

The response rates by baseline serostatus showed that all 95% CI were within -3.5% in the younger stratum with the same pattern as for the total study cohort. In the older stratum the 95% were within -8% except for MenC (-12.6%) for which the response rate among the baseline seropositive subset was slightly higher for the control vaccine.

At baseline the percentages of subjects with pre-vaccination rSBA titres ≥ 1:8 were high and ranged from 75.5% (MenW in ACWY-TT group) to 95.1% (MenA in ACWY-TT group). One month after vaccination, the percentages with titres ≥ 1:8 increased to at least 99.7% and percentages with ≥ 1:128 increased to at least 98.2% with no statistically significant differences between the two vaccines. The rSBA GMT values increased at least 9-fold after vaccination. GMTs adjusted for pre-vaccination measurements were statistically significantly higher in the ACWY-TT group. In addition, GMTs were statistically significantly higher in the conjugate vaccine group for MenA, W and Y in both age strata. For MenC the GMT was significantly higher in the conjugate vaccine group for those aged 11 to 17 years and numerically higher for those aged 18 to 55 years.

At one and two years after vaccination 473 and 458 subjects, respectively, were included in the ATP-I cohort.

The GMTs had dropped in all vaccine and age sub-groups but were still above baseline and the great majority had titres ≥1:128 vs. each meningococcal group. At least numerical advantages in terms of GMTs were maintained for the ACWY-TT group except against MenC in subjects aged 18-55 years. In addition, with the exception of MenC (both vaccines) and MenW135 (control group), the GMTs were at least numerically higher in the younger age stratum.

There was an additional analysis performed by the UK HPA using the HPA rSBA assay. Datasets generated for comparison were:

- o SELHPA: all subjects in with Y2 samples tested by HPA and for these subjects at earlier time points
- o SELGSK: results from GSK's rSBA for subjects with samples tested by HPA

On comparing the GMTs and the percentages with titres at least 1:128 it was very clear that at all times the GSK assay gave higher values than the HPA assay but there was a particularly large difference in the pre-vaccination values and also for the anti-W and anti-Y values throughout the study up to Y2.

For example, the percentages in the conjugate vaccine group deemed to be seronegative at baseline using the HPA assay for the four meningococcal groups ACWY were 93%, 90%, 97% and 71%, respectively. The corresponding percentages deemed to be seronegative at baseline using the GSK assay were 7%, 10%, 3% and 29%. Nevertheless, while post-vaccination titres were also higher using the GSK assay, the post-vaccination differences between groups considerably favoured the ACWY-TT vaccine using the HPA and GSK assays as shown below. The comparisons of GMTs showed the same pattern.

rSBA 2 years after vaccination (ATP cohort for persistence Year 2, SELHPA)

								Difference (ACWY-TT-MenPS)		
		ACWY-TT			MenPS				95% CI	
Antibody	**Type**	**N**	**n**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**
rSBA-MenA	1:8	99	94	94.9	98	90	91.8	3.11	-4.26	10.94
	1:128	99	92	92.9	98	86	87.8	5.17	-3.30	14.08
rSBA-MenC	1:8	100	98	98.0	99	86	86.9	11.13	4.29	19.47
	1:128	100	86	86.0	99	79	79.8	6.20	-4.39	16.89
rSBA-MenW-135	1:8	100	84	84.0	100	24	24.0	60.00	47.87	69.90
	1:128	100	80	80.0	100	19	19.0	61.00	48.88	70.81
rSBA-MenY	1:8	100	86	86.0	100	44	44.0	42.00	29.54	53.22
	1:128	100	82	82.0	100	36	36.0	46.00	33.19	57.20

rSBA 2 years after vaccination (ATP cohort for persistence Year 2, SELGSK)

								Difference ACWY-TT-MenPS		
		ACWY-TT			MenPS				95% CI	
Antibody	**Type**	**N**	**n**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**
rSBA-MenA	1:8	99	99	100	98	97	99.0	1.02	-2.75	5.57
	1:128	99	98	99.0	98	94	95.9	3.07	-1.87	9.17
rSBA-MenC	1:8	100	99	99.0	99	97	98.0	1.02	-3.64	6.20
	1:128	100	96	96.0	99	91	91.9	4.08	-2.88	11.70
rSBA-MenW-135	1:8	100	99	99.0	100	91	91.0	8.00	2.41	15.38
	1:128	100	98	98.0	100	81	81.0	17.00	9.34	26.07
rSBA-MenY	1:8	100	100	100	100	99	99.0	1.00	-2.74	5.47
	1:128	100	99	99.0	100	94	94.0	5.00	-0.14	11.63

Year 4 data from 019

Of the 500 subjects initially enrolled into study 015 426 returned for this Year 4 persistence phase: 317 primed with MenACWY-TT and 109 primed with *Mencevax* ACWY. Immunogenicity at Y4 was assessed for 420/426.

Among the 74 subjects who did not return there were 50 lost to follow-up, 22 were not willing to participate due to a reason other than an AE or SAE and 2 died due to causes unrelated to vaccination since the Y3 visit.

The mean age of subjects included in the ATP cohort for persistence at Y4 was 22.1 years with other demographics as shown below.

Synopsis Table 1: Study population (Total vaccinated cohort)

Number of subjects	**ACWY-TT**	**MenPS**
Planned, N	375	125
Randomised, N (Total Vaccinated Cohort)	317	109
Completed, n (%)	317 (100)	109 (100)
Demographics	**ACWY-TT**	**MenPS**
N (Total Vaccinated Cohort)	317	109
Females: Males	147:170	54:55
Mean Age, years (SD)	22.0 (7.72)	22.5 (8.62)
Asian - South East Asian heritage, n (%)	265 (83.6)	90 (82.6)

ACWY-TT = MenACWY-TT
MenPS = *Mencevax* ACWY

The median time elapsed since vaccination in study 015 was 210 weeks.

The analysis was based on the ATP cohort for antibody persistence at Y4 as follows:

- rSBA data were generated at all time points up to M36 (PRE, M1, M12, M24 and M36 post vaccination) at GSK laboratories for all subjects with sera available
- rSBA data were generated at the UK Health Protection Agency (HPA) laboratories for a subset of the samples at all time points (as above) except for M36
- **At M48** rSBA testing was performed **at HPA only and for all subjects** with available sera

As previously noted, the two rSBA assays (GSK vs. HPA) gave different results although the trends and overall conclusions drawn were compatible between the two sets of results. Due to the differences, the two sets of results have been presented in separate tables. As a result of the testing schema the antibody kinetics and decay from pre-vaccination and one month post-vaccination in 015 up to Y4 (M48) cannot be directly assessed due to the change in assay.

Based on the GSK assay results and testing sera up to Y3 (M36) the percentages with rSBA titres at least 1:128 remained >90% at M36 and the GMTs suggested a slowing of antibody decay between years 2 and 3 following the initial more rapid decline (see table below). The same pattern of observations applied to the ELISA results (IgG directed against capsular polysaccharides).

Table 8 **Percentage of subjects with GSK-rSBA titres equal to or above the cut-off values of 1:8 and 1:128 and GMTs at Month 0, 1 and Year 1, 2 and 3 (ATP cohort for persistence Year 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
GSK rSBA-MenA	ACWY-TT	PRE	281	267	95.0	91.8	97.2	250	89.0	84.7	92.4	329.4	282.1	384.7
		PI(M1)	299	299	100	98.8	100	298	99.7	98.2	100	4968.7	4450.4	5547.4
		PI(M12)	309	308	99.7	98.2	100	307	99.4	97.7	99.9	2106.9	1893.1	2344.8
		PI(M24)	301	300	99.7	98.2	100	298	99.0	97.1	99.8	1340.2	1201.7	1494.7
		PI(M36)	297	297	100	98.8	100	294	99.0	97.1	99.8	1253.3	1134.2	1384.8
	MenPS	PRE	93	81	87.1	78.5	93.2	74	79.6	69.9	87.2	228.3	159.3	327.3
		PI(M1)	104	104	100	96.5	100	103	99.0	94.8	100	2125.9	1768.9	2555.0
		PI(M12)	104	104	100	96.5	100	103	99.0	94.8	100	1110.4	928.8	1327.5
		PI(M24)	94	93	98.9	94.2	100	90	95.7	89.5	98.8	702.1	554.8	888.4
		PI(M36)	101	101	100	96.4	100	96	95.0	88.8	98.4	596.4	486.5	731.1
GSK rSBA-MenC	ACWY-TT	PRE	297	229	77.1	71.9	81.8	153	51.5	45.7	57.3	79.4	64.1	98.5
		PI(M1)	313	312	99.7	98.2	100	309	98.7	96.8	99.7	8988.6	7639.5	10576.0
		PI(M12)	308	307	99.7	98.2	100	300	97.4	94.9	98.9	1859.3	1614.0	2141.7
		PI(M24)	308	306	99.4	97.7	99.9	297	96.4	93.7	98.2	1151.0	997.6	1328.0
		PI(M36)	310	307	99.0	97.2	99.8	287	92.6	89.1	95.2	862.9	746.0	998.2
	MenPS	PRE	106	90	84.9	76.6	91.1	55	51.9	42.0	61.7	116.2	80.9	166.9
		PI(M1)	107	107	100	96.6	100	104	97.2	92.0	99.4	6056.8	4603.2	7969.5
		PI(M12)	105	104	99.0	94.8	100	101	96.2	90.5	99.0	1959.5	1435.8	2674.2
		PI(M24)	104	102	98.1	93.2	99.8	95	91.3	84.2	96.0	1197.0	836.4	1713.2
		PI(M36)	106	105	99.1	94.9	100	100	94.3	88.1	97.9	1124.5	812.1	1557.0
GSK rSBA-MenW-135	ACWY-TT	PRE	300	227	75.7	70.4	80.4	178	59.3	53.5	64.9	97.4	77.2	122.8
		PI(M1)	312	311	99.7	98.2	100	310	99.4	97.7	99.9	8660.9	7641.7	9815.9
		PI(M12)	311	310	99.7	98.2	100	309	99.4	97.7	99.9	3089.6	2671.0	3573.9
		PI(M24)	309	307	99.4	97.7	99.9	305	98.7	96.7	99.6	1973.9	1732.7	2248.6
		PI(M36)	309	308	99.7	98.2	100	305	98.7	96.7	99.6	2095.1	1817.0	2415.7
	MenPS	PRE	102	82	80.4	71.4	87.6	62	60.8	50.6	70.3	107.7	75.0	154.5
		PI(M1)	107	107	100	96.6	100	107	100	96.6	100	3028.4	2471.5	3710.8
		PI(M12)	107	107	100	96.6	100	101	94.4	88.2	97.9	714.0	571.3	892.3
		PI(M24)	103	92	89.3	81.7	94.5	82	79.6	70.5	86.9	312.1	217.6	447.7
		PI(M36)	102	88	86.3	78.0	92.3	81	79.4	70.3	86.8	327.4	218.4	490.8
GSK rSBA-MenY	ACWY-TT	PRE	304	283	93.1	89.6	95.7	244	80.3	75.3	84.6	319.2	268.2	380.0
		PI(M1)	312	312	100	98.8	100	311	99.7	98.2	100	10960.6	9859.2	12185.0
		PI(M12)	310	310	100	98.8	100	309	99.7	98.2	100	4436.2	3947.7	4985.1
		PI(M24)	309	308	99.7	98.2	100	306	99.0	97.2	99.8	3128.5	2747.7	3562.2
		PI(M36)	311	310	99.7	98.2	100	309	99.4	97.7	99.9	2641.8	2345.3	2975.9
	MenPS	PRE	106	99	93.4	86.9	97.3	84	79.2	70.3	86.5	311.5	229.8	422.1
		PI(M1)	107	107	100	96.6	100	107	100	96.6	100	4695.4	3939.9	5595.7
		PI(M12)	106	106	100	96.6	100	105	99.1	94.9	100	1444.8	1159.5	1800.2
		PI(M24)	103	103	100	96.5	100	99	96.1	90.4	98.9	891.4	713.8	1113.1
		PI(M36)	105	104	99.0	94.8	100	102	97.1	91.9	99.4	850.0	683.3	1057.2

The HPA data are shown in the next table up to Y4. Note carefully that up to M24 only a small fraction of the Y4 cohort had previously had sera tested using this assay so the results at Y4 pertain to a much larger number and the interpretation of the pattern in titres and GMTs over time must be viewed with caution. Nevertheless, at Y4 after vaccination:

- For rSBA-MenA titres ≥ 1:8 were present in 86.5% in the ACWY-TT group and 73.8% in the MenPS group.
- For rSBA-MenC titres ≥ 1:8 were present in 88.5% in the ACWY-TT group and 84.1% in the MenPS group.
- For rSBA-MenW-135 titres ≥ 1:8 were present in 74.0% in the ACWY-TT group and 25.2% in the MenPS group.
- For rSBA-MenY titres ≥ 1:8 were present in 82.8% in the ACWY-TT group and 43.9% in the MenPS group.

The rSBA GMTs in the ACWY-TT group ranged from 175.1 (rSBA-MenW-135) to 350.5 (rSBAMenY).

In the MenPS group rSBA, GMTs ranged from 11.3 (rSBA-MenW-135) to 315.0 (rSBAMenC).

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 0, 1 and Year 1, 2 and 4 (ATP cohort for persistence Year 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
HPA rSBA-MenA	ACWY-TT	PRE	29	1	3.4	0.1	17.8	1	3.4	0.1	17.8	2.3	1.7	3.1
		PI(M1)	29	29	100	88.1	100	29	100	88.1	100	4095.3	2614.7	6414.4
		PI(M12)	29	27	93.1	77.2	99.2	26	89.7	72.6	97.8	993.8	432.9	2281.6
		PI(M24)	88	83	94.3	87.2	98.1	81	92.0	84.3	96.7	741.4	495.4	1109.6
		PI(M48)	312	270	86.5	82.2	90.1	245	78.5	73.5	83.0	278.6	219.7	353.2
	MenPS	PRE	19	0	0.0	0.0	17.6	0	0.0	0.0	17.6	2.0	2.0	2.0
		PI(M1)	19	19	100	82.4	100	19	100	82.4	100	1463.2	886.5	2415.0
		PI(M12)	19	16	84.2	60.4	96.6	15	78.9	54.4	93.9	218.0	71.0	669.6
		PI(M24)	90	83	92.2	84.6	96.8	79	87.8	79.2	93.7	400.2	264.7	604.8
		PI(M48)	107	79	73.8	64.4	81.9	66	61.7	51.8	70.9	105.4	67.6	164.4
HPA rSBA-MenC	ACWY-TT	PRE	29	3	10.3	2.2	27.4	1	3.4	0.1	17.8	3.1	1.7	5.8
		PI(M1)	29	29	100	88.1	100	29	100	88.1	100	6420.0	4211.2	9787.2
		PI(M12)	29	28	96.6	82.2	99.9	24	82.8	64.2	94.2	427.6	220.3	830.1
		PI(M24)	91	89	97.8	92.3	99.7	78	85.7	76.8	92.2	293.6	219.6	392.6
		PI(M48)	312	276	88.5	84.4	91.8	254	81.4	76.6	85.6	273.6	220.6	339.4
	MenPS	PRE	16	0	0.0	0.0	20.6	0	0.0	0.0	20.6	2.0	2.0	2.0
		PI(M1)	16	16	100	79.4	100	16	100	79.4	100	9074.5	5318.2	15483.8
		PI(M12)	15	14	93.3	68.1	99.8	14	93.3	68.1	99.8	1927.5	638.9	5815.4
		PI(M24)	93	80	86.0	77.3	92.3	73	78.5	68.8	86.3	269.7	166.9	435.9
		PI(M48)	107	90	84.1	75.8	90.5	79	73.8	64.4	81.9	315.0	196.8	504.1
HPA rSBA-MenW-135	ACWY-TT	PRE	30	1	3.3	0.1	17.2	0	0.0	0.0	11.6	2.1	1.9	2.5
		PI(M1)	30	29	96.7	82.8	99.9	29	96.7	82.8	99.9	9571.6	4649.0	19706.4
		PI(M12)	30	28	93.3	77.9	99.2	27	90.0	73.5	97.9	1659.2	728.5	3778.7
		PI(M24)	90	77	85.6	76.6	92.1	73	81.1	71.5	88.6	283.0	174.8	458.0
		PI(M48)	312	231	74.0	68.8	78.8	214	68.6	63.1	73.7	175.1	131.5	233.0
	MenPS	PRE	18	3	16.7	3.6	41.4	1	5.6	0.1	27.3	3.9	1.8	8.7
		PI(M1)	17	13	76.5	50.1	93.2	13	76.5	50.1	93.2	738.8	129.9	4203.6
		PI(M12)	18	12	66.7	41.0	86.7	11	61.1	35.7	82.7	125.5	24.4	645.6
		PI(M24)	92	22	23.9	15.6	33.9	18	19.6	12.0	29.1	6.6	4.2	10.5
		PI(M48)	107	27	25.2	17.3	34.6	22	20.6	13.4	29.5	11.3	7.8	16.3
HPA rSBA-MenY	ACWY-TT	PRE	21	6	28.6	11.3	52.2	4	19.0	5.4	41.9	10.5	3.4	33.1
		PI(M1)	20	20	100	83.2	100	20	100	83.2	100	3126.8	1677.0	5830.2
		PI(M12)	21	20	95.2	76.2	99.9	18	85.7	63.7	97.0	968.5	392.4	2390.4
		PI(M24)	87	74	85.1	75.8	91.8	71	81.6	71.9	89.1	381.3	228.8	635.3
		PI(M48)	309	256	82.8	78.2	86.9	243	78.6	73.6	83.1	350.5	268.9	456.7
	MenPS	PRE	11	1	9.1	0.2	41.3	1	9.1	0.2	41.3	3.5	1.2	10.1
		PI(M1)	12	12	100	73.5	100	12	100	73.5	100	2663.0	1821.9	3892.4
		PI(M12)	12	6	50.0	21.1	78.9	4	33.3	9.9	65.1	22.3	3.4	146.2
		PI(M24)	92	40	43.5	33.2	54.2	32	34.8	25.1	45.4	18.3	10.6	31.6
		PI(M48)	107	47	43.9	34.3	53.9	37	34.6	25.6	44.4	26.0	16.6	40.7

The exploratory group comparisons of the HPA data suggested that 4 years after vaccination:

In the ACWY-TT group, the percentages of subjects with rSBA titres ≥ 1:8 and ≥ 1:128 were statistically significantly higher for MenA, MenW-135 and MenY serogroups.

Table 12 **Difference between groups in percentage of subjects with HPA-rSBA-MenA, HPA-rSBA-MenC, HPA-rSBA-MenW-135, HPA-rSBA-MenY titres equal to or above the cut-off values of 1:8 and 1:128, 4 years after the vaccination (ATP cohort for persistence Year 4)**

								Difference in percentage (ACWY-TT minus MenPS)		
		ACWY-TT			MenPS				95% CI	
Antibody	Type	N	n	%	N	n	%	%	LL	UL
HPA rSBA-MenA	≥ 1:8	312	270	86.5	107	79	73.8	12.71	4.19	22.43
	≥ 1:128	312	245	78.5	107	66	61.7	16.84	6.90	27.29
HPA rSBA-MenC	≥ 1:8	312	276	88.5	107	90	84.1	4.35	-2.69	13.04
	≥ 1:128	312	254	81.4	107	79	73.8	7.58	-1.22	17.50
HPA rSBA-MenW-135	≥ 1:8	312	231	74.0	107	27	25.2	48.80	38.57	57.60
	≥ 1:128	312	214	68.6	107	22	20.6	48.03	38.03	56.47
HPA rSBA-MenY	≥ 1:8	309	256	82.8	107	47	43.9	38.92	28.49	48.87
	≥ 1:128	309	243	78.6	107	37	34.6	44.06	33.55	53.58

In the ACWY-TT group, rSBA-MenA, rSBA-MenW-135 and rSBA-MenY GMTs were statistically significantly higher compared to the MenPS group.

Table 13 **GMT ratios between groups for HPA-rSBA-MenA, HPA-rSBA-MenC, HPA-rSBA-MenW-135, HPA-rSBA-MenY antibodies, 4 years after the vaccination (ATP cohort for persistence Year 4)**

					GMT ratio (ACWY-TT/MenPS)		
	ACWY-TT		MenPS			95% CI	
Antibody	N	GMT	N	GMT	Value	LL	UL
HPA rSBA-MenA	312	278.6	107	105.4	2.64	1.63	4.27
HPA rSBA-MenC	312	273.6	107	315.0	0.87	0.55	1.37
HPA rSBA-MenW-135	312	175.1	107	11.3	15.53	9.11	26.46
HPA rSBA-MenY	309	350.5	107	26.0	13.47	8.01	22.66

The results using each assay have also been presented according to the two initial age strata. Since this report focuses on Y4 only the HPA data are shown below.

Table 16 **Percentage of subjects with HPA-rSBA titres equal to or above the cut-off values of 1:8 and 1:128 and GMTs, per age strata at Month 0, 1 and Year 1, 2 and 4 (ATP cohort for persistence Year 4)**

					≥ 1:8				≥ 1:128				GMT		
							95% CI				95% CI			95% CI	
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
HPA rSBA-MenA	ACWY-TT	11-17y	PRE	29	1	3.4	0.1	17.8	1	3.4	0.1	17.8	2.3	1.7	3.1
			PI(M1)	29	29	100	88.1	100	29	100	88.1	100	4095.3	2614.7	6414.4
			PI(M12)	29	27	93.1	77.2	99.2	26	89.7	72.6	97.8	993.8	432.9	2281.6
			PI(M24)	62	59	95.2	86.5	99.0	57	91.9	82.2	97.3	783.0	483.2	1268.8
			PI(M48)	212	183	86.3	80.9	90.6	165	77.8	71.6	83.2	281.5	209.2	378.7
		18-55y	PI(M24)	26	24	92.3	74.9	99.1	24	92.3	74.9	99.1	650.8	297.3	1425.0
			PI(M48)	100	87	87.0	78.8	92.9	80	80.0	70.8	87.3	272.5	182.9	406.0
	MenPS	11-17y	PRE	19	0	0.0	0.0	17.6	0	0.0	0.0	17.6	2.0	2.0	2.0
			PI(M1)	19	19	100	82.4	100	19	100	82.4	100	1463.2	886.5	2415.0
			PI(M12)	19	16	84.2	60.4	96.6	15	78.9	54.4	93.9	218.0	71.0	669.6
			PI(M24)	64	60	93.8	84.8	98.3	58	90.6	80.7	96.5	485.0	307.1	765.9
			PI(M48)	75	57	76.0	64.7	85.1	47	62.7	50.7	73.6	111.4	65.3	190.1
		18-55y	PI(M24)	26	23	88.5	69.8	97.6	21	80.8	60.6	93.4	249.3	100.2	620.2
			PI(M48)	32	22	68.8	50.0	83.9	19	59.4	40.6	76.3	92.5	39.7	215.7
HPA rSBA-MenC	ACWY-TT	11-17y	PRE	29	3	10.3	2.2	27.4	1	3.4	0.1	17.8	3.1	1.7	5.8
			PI(M1)	29	29	100	88.1	100	29	100	88.1	100	6420.0	4211.2	9787.2
			PI(M12)	29	28	96.6	82.2	99.9	24	82.8	64.2	94.2	427.6	220.3	830.1
			PI(M24)	65	65	100	94.5	100	61	93.8	85.0	98.3	383.9	301.2	489.4
			PI(M48)	212	189	89.2	84.2	93.0	173	81.6	75.7	86.6	263.6	205.6	338.1
		18-55y	PI(M24)	26	24	92.3	74.9	99.1	17	65.4	44.3	82.8	150.2	67.7	333.3
			PI(M48)	100	87	87.0	78.8	92.9	81	81.0	71.9	88.2	296.1	194.1	451.8
	MenPS	11-17y	PRE	9	0	0.0	0.0	33.6	0	0.0	0.0	33.6	2.0	2.0	2.0
			PI(M1)	9	9	100	66.4	100	9	100	66.4	100	8690.2	3884.0	19443.7
			PI(M12)	8	7	87.5	47.3	99.7	7	87.5	47.3	99.7	1305.0	172.4	9880.8
			PI(M24)	66	55	83.3	72.1	91.4	50	75.8	63.6	85.5	228.1	125.1	415.8
			PI(M48)	75	62	82.7	72.2	90.4	53	70.7	59.0	80.6	235.6	133.8	414.9

		18-55y	PRE	7	0	0.0	0.0	41.0	0	0.0	0.0	41.0	2.0	2.0	2.0
			PI(M1)	7	7	100	59.0	100	7	100	59.0	100	9593.6	3729.3	24679.6
			PI(M12)	7	7	100	59.0	100	7	100	59.0	100	3010.2	813.2	11142.7
			PI(M24)	27	25	92.6	75.7	99.1	23	85.2	66.3	95.8	406.4	183.0	902.2
			PI(M48)	32	28	87.5	71.0	96.5	26	81.3	63.6	92.8	622.2	267.9	1445.1
HPA rSBA-MenW-135	ACWY-TT	11-17y	PRE	30	1	3.3	0.1	17.2	0	0.0	0.0	11.6	2.1	1.9	2.5
			PI(M1)	30	29	96.7	82.8	99.9	29	96.7	82.8	99.9	9571.6	4649.0	19706.4
			PI(M12)	30	28	93.3	77.9	99.2	27	90.0	73.5	97.9	1659.2	728.5	3778.7
			PI(M24)	65	56	86.2	75.3	93.5	54	83.1	71.7	91.2	327.2	186.7	573.3
			PI(M48)	212	162	76.4	70.1	82.0	152	71.7	65.1	77.7	216.7	153.0	306.9
		18-55y	PI(M24)	25	21	84.0	63.9	95.5	19	76.0	54.9	90.6	194.0	72.3	520.9
			PI(M48)	100	69	69.0	59.0	77.9	62	62.0	51.7	71.5	111.4	67.7	183.4
	MenPS	11-17y	PRE	8	0	0.0	0.0	36.9	0	0.0	0.0	36.9	2.0	2.0	2.0
			PI(M1)	8	6	75.0	34.9	96.8	6	75.0	34.9	96.8	687.1	32.4	14565.6
			PI(M12)	8	5	62.5	24.5	91.5	4	50.0	15.7	84.3	67.1	4.6	978.0
			PI(M24)	66	13	19.7	10.9	31.3	10	15.2	7.5	26.1	5.1	3.1	8.2
			PI(M48)	75	15	20.0	11.6	30.8	13	17.3	9.6	27.8	9.2	6.1	13.8
		18-55y	PRE	10	3	30.0	6.7	65.2	1	10.0	0.3	44.5	6.7	1.6	28.7
			PI(M1)	9	7	77.8	40.0	97.2	7	77.8	40.0	97.2	788.1	60.3	10303.2
			PI(M12)	10	7	70.0	34.8	93.3	7	70.0	34.8	93.3	207.0	17.6	2436.8
			PI(M24)	26	9	34.6	17.2	55.7	8	30.8	14.3	51.8	12.9	4.4	37.8
			PI(M48)	32	12	37.5	21.1	56.3	9	28.1	13.7	46.7	18.2	8.2	40.7

					≥ 1:8				≥ 1:128				GMT		
							95% CI				95% CI			95% CI	
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
HPA rSBA-MenY	ACWY-TT	11-17y	PRE	5	3	60.0	14.7	94.7	3	60.0	14.7	94.7	95.9	1.0	9393.8
			PI(M1)	4	4	100	39.8	100	4	100	39.8	100	12017.0	5185.5	27848.4
			PI(M12)	5	5	100	47.8	100	4	80.0	28.4	99.5	1170.7	53.3	25716.9
			PI(M24)	65	54	83.1	71.7	91.2	51	78.5	66.5	87.7	300.4	163.0	553.8
			PI(M48)	211	175	82.9	77.2	87.8	164	77.7	71.5	83.2	328.6	238.0	453.7
		18-55y	PRE	16	3	18.8	4.0	45.6	1	6.3	0.2	30.2	5.3	2.2	12.6
			PI(M1)	16	16	100	79.4	100	16	100	79.4	100	2233.2	1141.8	4367.8
			PI(M12)	16	15	93.8	69.8	99.8	14	87.5	61.7	98.4	912.8	332.8	2503.7
			PI(M24)	22	20	90.9	70.8	98.9	20	90.9	70.8	98.9	771.2	309.5	1921.5
			PI(M48)	98	81	82.7	73.7	89.6	79	80.6	71.4	87.9	402.6	251.4	644.7
	MenPS	11-17y	PRE	10	1	10.0	0.3	44.5	1	10.0	0.3	44.5	3.8	1.2	12.1
			PI(M1)	11	11	100	71.5	100	11	100	71.5	100	2792.7	1863.4	4185.5
			PI(M12)	11	5	45.5	16.7	76.6	3	27.3	6.0	61.0	15.8	2.3	105.8
			PI(M24)	66	26	39.4	27.6	52.2	22	33.3	22.2	46.0	15.8	8.2	30.4
			PI(M48)	75	34	45.3	33.8	57.3	26	34.7	24.0	46.5	24.9	15.0	41.5
		18-55y	PRE	1	0	0.0	0.0	97.5	0	0.0	0.0	97.5	2.0	-	-
			PI(M1)	1	1	100	2.5	100	1	100	2.5	100	1578.0	-	-
			PI(M12)	1	1	100	2.5	100	1	100	2.5	100	1023.0	-	-
			PI(M24)	26	14	53.8	33.4	73.4	10	38.5	20.2	59.4	26.6	9.4	75.4
			PI(M48)	32	13	40.6	23.7	59.4	11	34.4	18.6	53.2	28.7	11.2	73.8

As summarised in the tables below, at least numerically higher percentages within each age stratum in the conjugate vaccine group vs. unconjugated group still had titres at least 1:8 and at least 1:128 at Y4. The difference was especially marked for MenW and MenY. There was no consistent pattern between age strata in terms of higher or lower percentages with these titres at Y4 and they were mostly fairly comparable at this time point.

Table 19 **Difference between groups in percentage of subjects aged 11 to 17 years with HPA-rSBA-MenA, HPA-rSBA-MenC, HPA-rSBA-MenW-135, HPA-rSBA-MenY titres equal to or above the cut-off values of 1:8 and 1:128, 4 years after the vaccination (ATP cohort for persistence Year 4)**

								Difference in percentage (ACWY-TT/11-17y minus MenPS/11-17y)		
		ACWY-TT/11-17y			MenPS/11-17y				95% CI	
Antibody	Type	N	n	%	N	n	%	%	LL	UL
HPA rSBA-MenA	≥1:8	212	183	86.3	75	57	76.0	10.32	0.51	21.92
	≥1:128	212	165	77.8	75	47	62.7	15.16	3.38	27.70
HPA rSBA-MenC	≥1:8	212	189	89.2	75	62	82.7	6.48	-2.03	17.26
	≥1:128	212	173	81.6	75	53	70.7	10.94	0.14	23.09
HPA rSBA-MenW-135	≥1:8	212	162	76.4	75	15	20.0	56.42	44.54	65.91
	≥1:128	212	152	71.7	75	13	17.3	54.36	42.64	63.68
HPA rSBA-MenY	≥1:8	211	175	82.9	75	34	45.3	37.61	25.14	49.48
	≥1:128	211	164	77.7	75	26	34.7	43.06	30.36	54.36

Table 20 **Difference between groups in percentage of subjects aged 18 to 55 years with HPA-rSBA-MenA, HPA-rSBA-MenC, HPA-rSBA-MenW-135, HPA-rSBA-MenY titres equal to or above the cut-off values of 1:8 and 1:128, 4 years after the vaccination (ATP cohort for persistence Year 4)**

								Difference in percentage (ACWY-TT/18-55y minus MenPS/18-55y)		
		ACWY-TT/18-55y			MenPS/18-55y				95% CI	
Antibody	Type	N	n	%	N	n	%	%	LL	UL
HPA rSBA-MenA	≥1:8	100	87	87.0	32	22	68.8	18.25	2.74	36.67
	≥1:128	100	80	80.0	32	19	59.4	20.63	3.04	39.39
HPA rSBA-MenC	≥1:8	100	87	87.0	32	28	87.5	-0.50	-11.82	16.07
	≥1:128	100	81	81.0	32	26	81.3	-0.25	-13.82	17.72
HPA rSBA-MenW-135	≥1:8	100	69	69.0	32	12	37.5	31.50	11.75	48.81
	≥1:128	100	62	62.0	32	9	28.1	33.88	14.09	49.96
HPA rSBA-MenY	≥1:8	98	81	82.7	32	13	40.6	42.03	22.98	58.92
	≥1:128	98	79	80.6	32	11	34.4	46.24	26.94	62.31

Similar observations applied to the comparisons of GMTs by age stratum and vaccine group, as shown below.

Table 21 **GMT ratios between groups for HPA-rSBA antibodies in subjects aged 11 to 17 years, 4 years after the vaccination (ATP cohort for persistence Year 4)**

					GMT ratio (ACWY-TT/11-17y / MenPS/11-17y)		
	ACWY-TT/11-17y		MenPS/11-17y			95% CI	
Antibody	N	GMT	N	GMT	Value	LL	UL
HPA rSBA-MenA	212	281.5	75	111.4	2.53	1.40	4.55
HPA rSBA-MenC	212	263.6	75	235.6	1.12	0.66	1.91
HPA rSBA-MenW-135	212	216.7	75	9.2	23.58	12.54	44.33
HPA rSBA-MenY	211	328.6	75	24.9	13.18	7.10	24.45

MenPS = *Mencevax* ACWY
11-17y = subjects below 18 years of age
GMT = geometric mean antibody titre
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance); LL = lower limit, UL = upper limit

Table 22 **GMT ratios between groups for HPA-rSBA antibodies in subjects aged 18 to 55 years, 4 years after the vaccination (ATP cohort for persistence Year 4)**

					GMT ratio (ACWY-TT/18-55y / MenPS/18-55y)		
	ACWY-TT/18-55y		MenPS/18-55y			95% CI	
Antibody	N	GMT	N	GMT	Value	LL	UL
HPA rSBA-MenA	100	272.5	32	92.5	2.95	1.27	6.84
HPA rSBA-MenC	100	296.1	32	622.2	0.48	0.20	1.14
HPA rSBA-MenW-135	100	111.4	32	18.2	6.12	2.29	16.34
HPA rSBA-MenY	98	402.6	32	28.7	14.02	5.29	37.12

In the Total Cohort at Year 4 no SAEs related to vaccination or any events related to the lack of vaccine efficacy had been reported in the period between 6 months post vaccination and the Year 4 visit.

Seventeen pregnancies had been reported since the Year 3 visit of which 16 had resulted in a normal delivery and one subject had eclampsia. All pregnancies had a normal outcome (live infants with no apparent congenital anomaly). Up to the report cut-off date one additional pregnancy had been reported with normal delivery and normal outcome (live healthy infant).

5. Rapporteur's Overall Conclusion and Recommendation

Overall conclusion

Based on the more conservative HPA rSBA data, and noting that there are no hSBA data available from this study for comparison, the Y4 data indicate that > 80% of subjects retained at least rSBA titres 1:8 except for MenW135, for which the rates were 76% and 69% in the two age cohorts.

The antibody persistence data should be added to the SmPC along with the data from the other studies, as already planned by the MAH.

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.