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/P46/0036

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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Introduction

On 28th March, the MAH submitted a completed paediatric study MenACWY-TT-048 EXT039 Y4 for Nimenrix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The primary phase study MenACWY-TT-039, as well as the follow-up study after 2 years (MenACWY-TT-048 EXT039 Y2), were submitted as part of the initial MAA for Nimenrix. The Year 3 follow-up data in study MenACWY-TT-048 EXT039 Y3 were submitted under Article 46 in July 2012. Further follow-up of the subjects is planned up to one year after booster vaccination (administered 4 years after primary vaccination).

A variation application consisting of the full relevant data package (i.e containing several studies to update the labelling with available persistence data) were submitted and will be assessed within the scope of variation -09.

A short clinical expert statement has been provided.

The applicant 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 the above mentioned product and therefore do not require taking further regulatory action on the marketing authorisation for the above mentioned product.

Scientific discussion

Information on the development program

The MAH stated that the primary phase study MenACWY-TT-039, as well as the follow-up study after 2 years (MenACWY-TT-048 EXT039 Y2), were submitted as part of the initial MAA for Nimenrix. The Year 3 follow-up data in study MenACWY-TT-048 EXT039 Y3 were submitted under Article 46 in July 2012. Further follow-up of the subjects is planned up to one year after booster vaccination (administered 4 years after primary vaccination). A line listing of all the concerned studies was annexed.

Information on the pharmaceutical formulation used in the studies

As in initial MAA

Clinical aspects

1. Introduction

The MAH submitted report for:

- (MenACWY-TT-048 EXT039 Y2, 3, 4, 5) – Year 4 annex ;

2. Clinical study

The study 112036 (MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5) was a A phase III, open, multi-centre, controlled study to evaluate the long-term antibody persistence at 2 years, 3 years and 4 years after a single dose of GSK Biologicals' meningococcal serogroup A, C, W-135, Y- tetanus toxoid conjugate (MenACWY-TT) vaccine versus one dose of Meningitec™ administered in healthy 12 through 23-month old children who were primed in study MenACWY-TT-039 (109670) and to evaluate the

immunogenicity and safety of a booster dose of the same meningococcal conjugate vaccine as given in the primary study, 4 years after priming.

Methods

- Objective(s)

Primary:
Immunogenicity
At 48 months after primary vaccination of toddlers with MenACWY-TT or Meningitec vaccine, To evaluate the persistence of meningococcal antibodies in terms of percentage of subjects with serum bactericidal activity (using rabbit complement) rSBA titres ≥ 1:8 for each of the four serogroups.

Secondary:
Immunogenicity - Booster vaccination 4 years post primary vaccination:
One month after administration of the booster dose:

- To evaluate the immunogenicity of MenACWY-TT compared with *Meningitec* in terms of rSBA titre ≥ 1:128, rSBA, hSBA and anti-PS antibodies for serogroupC.

- To evaluate the fold increase in rSBA GMTs from pre-booster time-point (at Month 48) to postbooster time-point (at Month 49) for A, W-135 and Y serogroups.
- To evaluate the immunogenicity of MenACWY-TT in terms of rSBA, hSBA and anti-PS antibodies for A, W-135 and Y serogroups.

Immunogenicity - Persistence:
At 48 months after primary vaccination with a meningococcal conjugate vaccine and 12 months after booster vaccination:

- To evaluate the persistence of meningococcal A, C, W-135 and Y antibodies in terms of rSBA, serum bactericidal assay activity with human complement (hSBA) and anti-meningococcal polysaccharide (PS) antibodies for each of the four serogroups.

Safety - One month after the booster vaccine dose in both groups:

- To evaluate the safety and reactogenicity of MenACWY-TT and *Meningitec.*

- To describe unsolicited symptoms and serious adverse events (SAEs) during the 31-day period (Days 0-30) following vaccination.

The rSBA and hSBA testing of all blood samples was done at the laboratory of the Health Protection Agency (HPA) in the UK.

- Study design

Phase III, open, multi-centre and controlled study with two parallel groups. A blood sample was taken 48 months after the primary vaccination in study MenACWY-TT-039 (109670). At this same visit (month 48), a booster dose of the same vaccine that was given as the priming vaccine was administered. A second blood sample was taken one month later (month 49).

- Study population

Healthy male or female subjects having completed the primary study MenACWY-TT-039 (109670) and who were primed with MenACWY-TT or *Meningitec* vaccines, free of obvious health problems (including immunosuppressive or immunodeficient condition or bleeding disorders) as established by medical

history and clinical examination before entering into the study, without a history of meningococcal disease, who had not received a meningococcal polysaccharide or a meningococcal polysaccharide conjugate vaccine outside of study MenACWY-TT-039 (109670) or who had not received immunoglobulins and/or blood products within three months of study entry or another clinical study drug within 30 days of study entry. Written informed consent was obtained from the parent or guardian of the subject.

- Treatments

The subjects were enrolled in the following groups according to the meningococcal vaccine received in the primary vaccination study MenACWY-TT-039 (109670):

- ACWY-TT group (N=744 at most): consisting of subjects from both groups (MenACWYTT+MMRV and MenACWY-TT groups) vaccinated with MenACWY-TT in study MenACWYTT-039 (109670).

- MenCCRM group (N=248 at most): consisting of subjects from both groups (MMRV and *Meningitec* groups) vaccinated with *Meningitec* in study MenACWY-TT-039 (109670). All subjects were to be boosted at Month 48 (4 years after primary vaccination) with the same meningococcal vaccine as given in the primary study.

- Statistical Methods

For each treatment group, at approximately 36 months after primary vaccination, for each antigen assessed:

- Geometric mean titres (GMTs) with 95% CIs were tabulated for titres in all subjects.

- Percentages of subjects with titres above proposed cut-offs with 95% confidence intervals (CIs) were calculated.

- The distribution of concentrations or titres was also tabulated and evaluated using reverse cumulative curves for each antibody.

Modelling prediction

This analysis was performed at Month 48 persistence time-point, in the ACWY-TT group for rSBA and hSBA-MenA, W-135 and Y, and in both groups for rSBA-MenC and hSBA-MenC. In order to complement the descriptive analyses of observed persistence per time point, GSK performed a longitudinal analysis.

Results

- Study population

Across the two vaccine groups, the mean age of the subjects in the According-to-protocol (ATP) cohort for persistence Year 4 was 63.7 months (range 60 to 69 months). The distribution of males and females was similar (50.7% male and 49.3% female). The majority of the subjects in each group where White/Caucasian/European heritage (99.6%). The demographics for the Booster ATP cohort for immunogenicity were similar to the ATP cohort for persistence at Month 48.

Number of subjects	ACWY-TT	MenCCRM
Planned, N	452	151
Randomised, N (Total Cohort)	246	48
Completed, n (%)	246 (100)	48 (100)
Demographics	**ACWY-TT**	**MenCCRM**
N (Total Cohort)	246	48
Females:Males	120:126	22:26
Mean Age, months (SD)	63.7 (1.81)	63.9 (1.97)
White - Caucasian / European heritage, n (%)	245 (99.6)	47 (97.9)
Synopsis Table 2: Demography (Booster Total Vaccinated cohort)		
Number of subjects	**ACWY-TT**	**MenCCRM**
Planned, N	452	151
Randomised, N (Booster Total Vaccinated Cohort)	245	48
Completed, n (%)	244 (99.6)	47 (97.9)
Demographics	**ACWY-TT**	**MenCCRM**
N (Booster Total Vaccinated Cohort)	245	48
Females:Males	119:126	22:26
Mean Age, months (SD)	63.7 (1.81)	63.9 (1.97)
White - Caucasian / European heritage, n (%)	244 (99.6)	47 (97.9)
ACWY-TT = Pooled Co-ad and ACWY-TT groups from primary study 109670 (MenACWY-TT-039) MenCCRM = Pooled MMRV and MenCCRM groups from primary study 109670 (MenACWY-TT-039) N = total number of subjects n (%) = number / percentage of subjects in a given category SD = standard deviation Note: Three subjects that participated in the Year 4 persistence (Month 48) did not return for Month 49. One subject was diagnosed with asthma and was not vaccinated (pid 541); one subject was vaccinated at M48 but moved out of the area, however, this subject did return the diary card with a reported solicited and unsolicited symptom (pid 852); another subject was lost-to-follow up (pid 893).		

- Immunogenicity results

Immunogenicity:

Immunogenicity analysis was performed on the ATP cohort for persistence at Year 4. No confirmatory analyses were performed on primary or secondary objectives for the persistence phase.

- At 48 months after primary vaccination in study MenACWY-TT-039, primary analysis showed HPA rSBA-MenA, HPA rSBA-MenC, HPA rSBA-MenW-135 and HPA rSBA-MenY titres ≥1:8 was 74.1%, 40.4%, 49.3% and 58.2% in the ACWY-TT group and 28.9%, 35.6%, 15.6% and 24.4% in the MenCCRM group, respectively.

- At 48 months after primary vaccination, the percentage of subjects with hSBA-MenA, hSBAMenC, hSBA-MenW-135 and hSBA-MenY titres ≥1:4 was 29.3%, 73.7%, 81.2% and 65.4% in the ACWY-TT group and 14.3%, 46.9%, 7.7% and 22.2% in the MenCCRM group, respectively.

- At 48 months after primary vaccination, the percentage of subjects with HPA anti-PSA, HPA anti-PSC, HPA anti-PSW-135 and HPA anti-PSY concentrations ≥0.3μg/mL was 100%, 28.6%, 100% and 96.0% in the ACWY-TT group and 90.9%, 33.3%, 77.3% and 90.0% in the MenCCRM group, respectively. The analysis of the immunogenicity using the Total cohort at Month 48 was consistent with the ATP cohort for persistence at Month 48.

One month after booster vaccination (Month 49)

Immunogenicity analysis was performed on the Booster ATP cohort for Immunogenicity. No confirmatory analyses were performed on primary or secondary objectives for the booster phase.

- At Month 49, one month after the booster dose, the percentage of subjects with HPA rSBA-MenA, HPA rSBA-MenC, HPA rSBA-MenW-135 and HPA rSBA-MenY titres ≥1:8 and ≥1:128 was 100% in the ACWY-TT group and 100% for HPA rSBA-MenC in the MenCCRM group.

- At Month 49, one month after the booster dose, the percentage of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY titres ≥1:4 and ≥1:8 was 99.5%, 100%, 100%, 100%, respectively, in the ACWY-TT group and 100% for hSBA-MenC in the MenCCRM group.

- At Month 49, one month post-booster, hSBA GMTs were 52 to 272 times higher compared to one month post-primary hSBA GMTs. Because of the change in assay the same assessment could not be made for the rSBA GMTs.

- At Month 49, post-booster rSBA GMTs and hSBA GMTs were 65 to 365 times and 227 to 704 times higher, respectively, compared to pre-booster GMTs.

- At Month 49, one month after the booster dose, the percentage of subjects with HPA anti-PSA, HPA anti-PSC, HPA anti-PSW-135 and HPA anti-PSY concentrations ≥0.3μg/mL was 100%, 100%, 100%, 98.4%, respectively, in the ACWY-TT group and 100% for HPA anti-PSC in the MenCCRM group. The percentage of subjects with HPA anti-PSA, HPA anti-PSC, HPA anti-PSW-135 and HPA anti-PSY concentrations ≥2.0 μg/mL was 98.5%, 95.7%, 100%, 98.4%, respectively, in the ACWY-TT group and 100% for HPA anti-PSC in the MenCCRM group.

- At Month 49, one month after the booster dose, the percentage of subjects with a booster response for HPA rSBA-MenA, HPA rSBA-MenC, HPA rSBA-MenW-135 and HPA rSBA-MenY titres was 90.5%, 95.8%, 98.6%, 97.7%, respectively, in the ACWY-TT group and 88.4% for HPA rSBA-MenC in the MenCCRM group.

- At Month 49, one month after the booster dose, the percentage of subjects with a booster response for hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY was 100%, 93.8%, 99.3%, 98.1%, respectively, in the ACWY-TT group and 90.3% for hSBA-MenC in the MenCCRM group.

The analysis of the immunogenicity using the Booster Total vaccinated cohort was consistent with the one using the Booster ATP cohort for immunogenicity.

Percentage of subjects with GSK rSBA titers equal to or above the cut-off values of 1:8 and 1:128 and GMTs at pre, 42 days post, and 24 months post-primary vaccination (ATP cohort for persistence at Month 48)

				≥ 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	103	36	35.0	25.8	45.0	25	24.3	16.4	33.7	15.1	10.4	22.1
		POST	221	221	100	98.3	100	221	100	98.3	100	2041.5	1833.0	2273.7
		M24	188	185	98.4	95.4	99.7	175	93.1	88.5	96.3	437.1	376.6	507.4
	MenCCRM	PRE	20	5	25.0	8.7	49.1	1	5.0	0.1	24.9	8.5	4.4	16.5
		POST	21	12	57.1	34.0	78.2	7	33.3	14.6	57.0	29.0	12.6	66.7
		M24	35	29	82.9	66.4	93.4	22	62.9	44.9	78.5	106.4	58.8	192.4
rSBA-MenC	ACWY-TT	PRE	105	32	30.5	21.9	40.2	15	14.3	8.2	22.5	11.2	8.1	15.4
		POST	220	220	100	98.3	100	208	94.5	90.7	97.2	475.7	425.3	532.2
		M24	194	175	90.2	85.1	94.0	97	50.0	42.8	57.2	105.4	84.6	131.3
	MenCCRM	PRE	19	6	31.6	12.6	56.6	1	5.3	0.1	26.0	9.3	4.9	17.9
		POST	45	43	95.6	84.9	99.5	25	55.6	40.0	70.4	154.6	103.6	230.6
		M24	36	24	66.7	49.0	81.4	18	50.0	32.9	67.1	53.6	27.1	105.8
rSBA-MenW-135	ACWY-TT	PRE	113	57	50.4	40.9	60.0	26	23.0	15.6	31.9	21.0	15.2	29.1
		POST	221	221	100	98.3	100	221	100	98.3	100	2361.5	2112.8	2639.4
		M24	194	192	99.0	96.3	99.9	177	91.2	86.3	94.8	398.2	343.1	462.1
	MenCCRM	PRE	26	13	50.0	29.9	70.1	6	23.1	9.0	43.6	23.0	10.5	50.3
		POST	24	16	66.7	44.7	84.4	7	29.2	12.6	51.1	41.2	18.3	93.1
		M24	36	22	61.1	43.5	76.9	17	47.2	30.4	64.5	49.1	23.5	102.5
rSBA-MenY	ACWY-TT	PRE	118	75	63.6	54.2	72.2	50	42.4	33.3	51.8	53.2	36.2	78.2
		POST	220	220	100	98.3	100	220	100	98.3	100	2668.6	2352.4	3027.3
		M24	195	190	97.4	94.1	99.2	163	83.6	77.6	88.5	411.1	336.1	502.9
	MenCCRM	PRE	26	18	69.2	48.2	85.7	13	50.0	29.9	70.1	67.4	28.7	158.0
		POST	25	18	72.0	50.6	87.9	12	48.0	27.8	68.7	72.2	30.7	169.8
		M24	37	31	83.8	68.0	93.8	25	67.6	50.2	82.0	186.9	98.1	355.8

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

Percentage of subjects with HPA rSBA titers equal to or above the cut-off values of 1:8 and 1:128 and GMTs at 36 and 48 months post-primary vaccination (ATP cohort for persistence at Month 48)

				≥ 1:8				≥ 1:128				GMT		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
rSBA-MenA	ACWY-TT	M36	213	131	61.5	54.6	68.1	48	22.5	17.1	28.7	19.4	15.5	24.3
		M48	224	166	74.1	67.9	79.7	134	59.8	53.1	66.3	107.3	77.6	148.3
	MenCCRM	M36	41	3	7.3	1.5	19.9	3	7.3	1.5	19.9	5.3	3.8	7.4
		M48	45	13	28.9	16.4	44.3	12	26.7	14.6	41.9	18.4	8.5	39.7
rSBA-MenC	ACWY-TT	M36	213	69	32.4	26.2	39.1	15	7.0	4.0	11.3	8.5	7.1	10.3
		M48	225	91	40.4	34.0	47.2	34	15.1	10.7	20.5	12.3	9.8	15.3
	MenCCRM	M36	41	6	14.6	5.6	29.2	3	7.3	1.5	19.9	5.9	4.2	8.3
		M48	45	16	35.6	21.9	51.2	10	22.2	11.2	37.1	13.5	7.4	24.5
rSBA-MenW-135	ACWY-TT	M36	212	110	51.9	44.9	58.8	74	34.9	28.5	41.7	27.1	20.1	36.5
		M48	225	111	49.3	42.6	56.1	88	39.1	32.7	45.8	30.5	22.4	41.5
	MenCCRM	M36	41	2	4.9	0.6	16.5	2	4.9	0.6	16.5	5.1	3.6	7.1
		M48	45	7	15.6	6.5	29.5	7	15.6	6.5	29.5	8.0	4.8	13.3
rSBA-MenY	ACWY-TT	M36	213	118	55.4	48.5	62.2	63	29.6	23.5	36.2	24.2	18.5	31.6
		M48	225	131	58.2	51.5	64.7	91	40.4	34.0	47.2	36.2	27.1	48.4
	MenCCRM	M36	41	6	14.6	5.6	29.2	2	4.9	0.6	16.5	6.0	4.2	8.5
		M48	45	11	24.4	12.9	39.5	9	20.0	9.6	34.6	10.4	6.0	18.0

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

Robustness modelling

The robustness analysis models provided estimated GMTs for rSBA-MenA, rSBA-MenW-135, rSBAMenY, hSBA-MenA, hSBA-MenW-135 and hSBA-MenY in the ACWY-TT group and rSBA-MenC and hSBA-MenC in both groups that were within 2-fold of the observed values. This indicates that the initial analysis performed at each time-point separately (i.e. in each study) does not seem to be unduly affected by subjects who dropped out. Additionally, the modelling also shows that the observed values were not biased by different rates of dropout in the two groups due to revaccination.

- Safety results

The safety analysis for the persistence phase was performed on the Total vaccinated cohort Month 48.

No unsolicited adverse events were collected during the year 4 persistence phase of the study.

Serious adverse events:
No serious adverse events (SAEs) considered to be possibly related to vaccination by the investigator related to study participation, related to GSK concomitant medication or fatal SAEs were reported in the period between the last visit in the primary study (MenACWY-TT-039) and the Year 4 persistence visit.

Withdrawals due to adverse events /serious adverse events:
No subject withdrew because of an AE or SAE during the year 4 persistence phase of the study.

Booster phase (Month 49)

The safety analysis for the Booster phase was performed on the Booster Total vaccinated cohort.

Overall incidence of AEs:

During the 8-day follow-up period after the booster dose, at least one symptom (solicited or unsolicited) was reported in 77.6% of subjects in the ACWY-TT group and in 81.3% of the subjects in the MenCCRM group. Grade 3 symptoms were reported in 21.2% and 12.5% of subjects in the ACWY-TT and MenCCRM groups, respectively. In both groups, the majority of grade 3 symptoms were local, with only 2.4% of subjects in the ACWY-TT group and none in the MenPS group reporting grade 3 general symptoms.

Solicited local AEs:

Pain was the most frequently reported solicited local symptom during the 8-day follow-up period in both groups (61.1% of subjects in the ACWY-TT group and 48.9% of subjects in the MenCCRM group) with grade 3 pain reported in 0.4% of subjects in the ACWY-TT group and no grade 3 pain reported in the MenCCRM group. Redness was reported equally in both groups (36.9% and 36.2% in the ACWY-TT and MenCCRM groups, respectively) with grade 3 redness being reported in 16.0% of subjects in the ACWY-TT group and 10.6% in the MenCCRM group. Swelling was reported in 28.7% of subjects in the ACWY-TT group and 23.4% of subjects in the MenCCRM group. Grade 3 swelling was reported in 11.1% of subjects in the ACWY-TT group and 4.3% of subjects in the MenCCRM group. No medical advice was sought for any of the local symptoms.

Solicited general AEs:

Drowsiness and irritability were the most frequently and equally reported solicited general symptoms during the 8-day follow-up period in both groups. Drowsiness was reported in 16.8% and 21.3% of subjects in the ACWY-TT and MenCCRM groups, respectively. Irritability was reported in 16.4% and 23.4% of subjects in the ACWY-TT group and MenCCRM group, respectively. No grade 3 symptoms for drowsiness or irritability were reported for either group. Loss of appetite was reported in 12.7% of subjects in the ACWY-TT group and 17.0% of subjects in the MenCCRM group. Grade 3 loss of appetite was reported in 0.8% of subjects in the ACWY-TT group with no grade 3 loss of appetite reported in the MenCCRM group. Any fever was reported in 6.6% of subjects in the ACWY-TT group and 2.1% of subjects in the MenCCRM group. Only two subjects in the ACWY-TT group and no subjects in the MenPS group had fever >39.5.

Unsolicited AEs:

At least one unsolicited symptom was reported by 43.3 % of subjects in the ACWY-TT group and 37.5% in the MenCCRM group during the 31-day period after booster vaccination. Each specific grade 3 unsolicited event was reported infrequently (≤0.8%) in the ACWY-TT group. No grade 3 unsolicited symptoms were reported in the MenCCRM group. Vaccine related unsolicited symptoms were reported in 19.2% of subjects in the ACWY-TT group and in 2.1% of subjects in the MenCCRM group. No grade 3 vaccine related unsolicited symptoms were reported in either group.

Serious adverse events:

SAEs were reported for two subjects (0.8%) in the ACWY-TT group during the 31 day follow-up period. The first subject (pid=80) had a thumb injury and was hospitalised. The second subject (pid=134) had an allergic reaction which required an emergency room visit. Both SAEs were resolved and were not considered to be causally related to vaccination. There were no SAEs reported in the MenCCRM group.

Withdrawals due to adverse events /serious adverse events:

No subject withdrew because of an AE or SAE during the booster phase of the study.

3. Discussion on clinical aspects

Immunogenicity:

- At 48 months after the primary vaccination in study MENACWY-TT-039, the percentage of subjects with HPA rSBA-MenA, HPA rSBA-MenC, HPA rSBA-MenW-135 and HPA rSBAMenY titres ≥ 1:8 were 74.1%, 40.4%, 49.3% and 58.2% in the ACWY-TT group and 28.9%, 35.6%, 15.6% and 24.4% in the MenCCRM group, respectively.

- At Month 49, one month after the booster dose, the percentage of subjects with HPA rSBA-MenA, HPA rSBA-MenC, HPA rSBA-MenW-135 and HPA rSBA-MenY titres ≥1:8 and ≥1:128 was 100% in the ACWY-TT group and 100% for HPA rSBA-MenC in the MenCCRM group.

- At Month 49, one month after the booster dose, the percentage of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY titres ≥1:4 and ≥1:8 was 99.5%, 100%, 100%, 100%, respectively, in the ACWY-TT group and 100% for hSBA-MenC in the MenCCRM group.

Overall, the Y4 data confirmed modest declines of SBA titres for all serogroups but titres for type C were still numerically higher than those observed following priming with MenCCRM. The booster has resulted in reconstitution of titres against all serogroups.

Safety:

The booster given at Y4 was relatively well tolerated. The pattern of reactogenicity and safety observed in the study was similar to the one previously reported during MAA and reflected in the SmPC. No new safety concerns were identified.

The data from Y4 persistence provided with this submission are also being evaluated within the Variation 009 with consequential update of section 5.1 and inclusion of the data into

Rapporteur's overall conclusion and recommendation

Clinical data from extension phase of MENACWY-TT-039 (MENACWY-TT-048) are considered supportive to persistence of SBA responses at Y4 in children who were primed at age of 12-23 months. The study has been submitted as a part of currently assessed variation -09 and request for consequential to variation update of section 5.1 is accepted.

☒ **Fulfilled –**

No further action required, however further data were provided in the context of a variation prior any conclusion on product information amendments is made.

Additional clarifications requested

Not applicable