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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/P46/0034
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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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Introduction

On 28th March, the MAH submitted a completed paediatric study MenACWY-TT-043 EXT036 for Nimenrix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The applicant states that the above mentioned study is part of a clinical development program. MenACWY-TT-043 EXT036 Y3 and Y4 represents the follow-up to Year 3 and 4 of subjects who were initially enrolled into the primary study MenACWY-TT-036. The primary phase study MenACWY-TT-036, as well as the follow-up study after 2 years (MenACWY-TT 043 EXT 036 Y2) were submitted as part of the initial MAA for Nimenrix. Further follow-up of the subjects is planned up to 5 years following primary vaccination in MenACWY-TT-036.

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 MenACWY-TT-043 EXT036 Y3 and Y4 are parts of a clinical development program. The study has two stages: the vaccination stage (MenACWY-TT-036) and the long-term persistence stage (MenACWY-TT-043 EXT: 036 Y2, 3, 4 and 5) with assessments of long-term protection at 2, 3, 4 and 5 years after vaccination. The vaccination stage of the study along with antibody persistence at Y2 were assessed as a part of initial MAA and Y3 data are provided with current submission. A full report describing the persistence results for years 2 through 5 after primary vaccination of Nimenrix will be written once the results of the Year 5 persistence study are available. 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 interim reports for:

- MenACWY-TT-043 EXT036 Y3;
- MenACWY-TT-043 EXT036 Y4;

2. Clinical study

The study 112148 (MENACWY-TT-043 EXT 036 Y2, 3, 4) was a phase III, open, controlled study to assess the persistence of antibodies after one dose of GlaxoSmithKline Biologicals' meningococcal serogroup ACWY conjugate vaccine (MenACWY-TT) given intramuscularly versus one dose of *Mencevax*™ ACWY given subcutaneously to healthy subjects aged 11 through 17 years in the primary study.

Methods

- Objective(s)

Primary:
Immunogenicity
At 36 and 48 months after primary vaccination of adolescents with MenACWY-TT or Mencevax ACWY 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
At 36 and 48 months after primary vaccination of adolescents with MenACWY-TT or Mencevax ACWY vaccine, to evaluate the persistence of meningococcal A, C, W-135 and Y antibodies in terms of rSBA titres for each of the four serogroups.

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

- Study design

Phase III, open, randomised, multi-centre and controlled study with two parallel groups. One blood sample was collected for each subject at 36 and 48 months after primary vaccination in study 109069 (MenACWY-TT-036).

- Study population /Sample size

The Total cohort at Month 36 and 48 included all subjects who received their complete vaccination course in study 109069 (MENACWY-TT-036) and who came back for appropriate follow-up visits.

- Treatments

The subjects were randomised with a 3:1 ratio to either group ACWY-TT or group MenPS in the primary study 109069 (MENACWY-TT-036):

- Group ACWY-TT: subjects received one dose of MenACWY-TT in the primary vaccination study 109069 (MENACWY-TT-036).

- Group MenPS: subjects received one dose of *Mencevax* ACWY in the primary vaccination study 109069 (MENACWY-TT-036).

- 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 rSBA-MenA, rSBA-MenC, rSBAMenW-

135 and rSBA-MenY in all subjects.

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

- The persistence of antibody titres was presented using reverse cumulative curves.
For each of the serogroups, an exploratory evaluation of the differences in the immune response at approximately 36 months after the primary vaccination was performed in terms of:

- Differences in the percentage of subjects with rSBA antibody titres ≥ 1:8 and 1:128 with standardized asymptotic 95% CIs and the ratio of the GMTs with 95% CIs between group ACWYTT and group MenPS.
Exploratory group comparisons were examined as follows: the exclusion of 1 from the 95% CI on the GMT ratios or 0% from the 95% CI on the differences in percentage of subjects with rSBA titres ≥ 1:8 and 1:128 was used to highlight potential group differences. However, these potential differences should be interpreted with caution considering that there was no adjustment for multiplicity for these comparisons and that the clinical relevance of any differences was not accounted for in the planning of the exploratory analyses.

Results

- Study population

Of the 790 subjects who were enrolled and randomised in India and the Philippines in study MENACWY-TT-036 (109069), 643 subjects participated in the Month 36 persistence visit. Of the 643 subjects in the Total cohort at Month 36, 17 subjects (16 in group ACWY-TT and 1 in group MenPS) were eliminated from the ATP Cohort for Persistence Month 36 (N=626):

- 15 subjects (14 in group ACWY-TT and 1 in group MenPS) were not compliant with the blood sampling schedule. The blood sample was taken from 1 to 7 weeks too late.

- 2 subjects in group ACWY-TT had essential serological data missing. One subject came for the visit, but did not have a blood sample taken; the other subject had a blood sample taken but the volume of serum was insufficient to perform the laboratory testing.

Of the 790 subjects who were enrolled and randomised in India and the Philippines in study MENACWY-TT-036 (109069), 541 subjects participated in the Month 48 persistence visit. Of the 541 subjects in the Total cohort at Month 48, 5 subjects (4 in the ACWY-TT group and 1 in the MenPS group) were eliminated from the ATP cohort for persistence at Month 48 (N=536) as they were not compliant with the blood sampling schedule. The blood sample was taken from 4 weeks too early to 2 weeks too late.

Study population (Total vaccinated cohort)		
Number of subjects	**ACWY-TT**	**MenPS**
Planned, N	374	124
Enrolled, N (Total cohort at Month 36)	488	155
Completed, n (%)	488 (100)	155 (100)
Demographics	**ACWY-TT**	**MenPS**
N (Total cohort at Month 36)	488	155
Females:Males	256:232	80:75
Mean Age, years (SD)	17.3 (1.96)	17.3 (1.98)
Asian - South East Asian heritage, n (%)	294 (60.2)	97 (62.6)
ACWY-TT = MenACWY-TT, MenPS = *Mencevax* ACWY		

Number of subjects	ACWY-TT	MenPS
Planned, N	299	99
Enrolled, N (Total cohort at Month 48)	407	134
Completed, n (%)	404 (99.3)	132 (98.5)
Demographics	**ACWY-TT**	**MenPS**
N (Total cohort at Month 48)	407	134
Females:Males	212:195	68:66
Mean Age, years (SD)	18.1 (2.01)	18.1 (1.96)
Asian - South East Asian heritage, n (%)	293 (72.0)	97 (72.4)

- Immunogenicity results

Immunogenicity:

The immunogenicity analysis was performed on the ATP cohort for persistence at Month 36. Because for any vaccine group, fewer than 5% of the subjects with serological results were eliminated from the ATP cohort for persistence at Month 36, an analysis on the Total cohort at Month 36 was not performed.

- At Month 36, the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres ≥ 1:8 was 93.2%, 91.5%, 82.4% and 93.4%, respectively, in group ACWY-TT and was 83.1%, 86.4%, 30.5% and 57.8%, respectively, in group MenPS.
- At Month 36, the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres ≥ 1:128 was 89.2%, 85.0%, 78.6% and 89.4%, respectively, in group ACWYTT and was 79.2%, 78.6%, 24.7% and 51.3% for rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY, respectively, in group MenPS.
- The exploratory group comparison suggested a higher percentage of subjects with rSBA-MenA,rSBA-MenW-135 and rSBA-MenY titres ≥ 1:8 and ≥ 1:128 and a higher rSBA-MenA, rSBAMenW-135 and rSBA-MenY GMT in group ACWY-TT than in group MenPS (lower limit of the 95% CI on the difference in percentage of subjects with titres ≥ 1:8 and ≥ 1:128 is above 0% and lower limit of 95% CI on the GMT ratio is above 1). Refer to section 'Primary and secondary exploratory analysis' for the reliability of such analyses.

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 36 (ATP cohort for persistence at Month 36)

				≥ 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(M36)	472	440	93.2	90.6	95.3	421	89.2	86.0	91.8	470.2	402.1	549.8
	MenPS	PI(M36)	154	128	83.1	76.2	88.7	122	79.2	72.0	85.3	211.9	152.7	294.1
rSBA-MenC	ACWY-TT	PI(M36)	472	432	91.5	88.6	93.9	401	85.0	81.4	88.1	375.6	314.8	448.1
	MenPS	PI(M36)	154	133	86.4	79.9	91.4	121	78.6	71.2	84.8	407.0	275.7	600.8
rSBA-MenW-135	ACWY-TT	PI(M36)	472	389	82.4	78.7	85.7	371	78.6	74.6	82.2	352.6	282.0	440.9
	MenPS	PI(M36)	154	47	30.5	23.4	38.4	38	24.7	18.1	32.3	16.4	11.2	24.1
rSBA-MenY	ACWY-TT	PI(M36)	472	441	93.4	90.8	95.5	422	89.4	86.3	92.0	752.3	633.3	893.6
	MenPS	PI(M36)	154	89	57.8	49.6	65.7	79	51.3	43.1	59.4	68.5	44.2	106.1

ACWY-TT = MenACWY-TT
MenPS = *Mencevax* ACWY
GMT = geometric mean titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PI(M36) = Post-primary vaccination at Month 36

The immunogenicity analysis was performed on the ATP cohort for persistence at Month 48. Since for any vaccine group, fewer than 5% of the subjects with serological results were eliminated from the ATP cohort for persistence at Month 48, an analysis on the Total cohort at Month 48 was not performed.

- At Month 48, the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres ≥1:8 was 90.1%, 94.3%, 77.4% and 89.5%, respectively, in the ACWY-TT group and was 80.5%, 87.2%, 27.3% and 48.5%, respectively, in the MenPS group.

Percentage of subjects with HPA rSBA titres equal to or above the cut-off values of 1:8 and 1:128 and GMTs from Month 36 up to Month 48 (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	PI(M36)	399	369	92.5	89.4	94.9	351	88.0	84.4	91.0	417.8	351.6	496.5
		PI(M48)	403	363	90.1	86.7	92.8	344	85.4	81.5	88.7	375.7	312.4	451.7
	MenPS	PI(M36)	132	107	81.1	73.3	87.4	101	76.5	68.4	83.5	168.2	118.2	239.2
		PI(M48)	133	107	80.5	72.7	86.8	101	75.9	67.8	82.9	171.4	119.6	245.6
rSBA-MenC	ACWY-TT	PI(M36)	399	363	91.0	87.7	93.6	338	84.7	80.8	88.1	353.0	291.9	427.0
		PI(M48)	402	379	94.3	91.5	96.3	359	89.3	85.9	92.2	376.7	319.6	444.0
	MenPS	PI(M36)	132	111	84.1	76.7	89.9	99	75.0	66.7	82.1	325.9	210.6	504.6
		PI(M48)	133	116	87.2	80.3	92.4	107	80.5	72.7	86.8	368.7	248.0	548.2
rSBA-MenW-135	ACWY-TT	PI(M36)	399	324	81.2	77.0	84.9	307	76.9	72.5	81.0	288.6	227.0	367.0
		PI(M48)	402	311	77.4	73.0	81.4	292	72.6	68.0	76.9	208.2	163.3	265.3
	MenPS	PI(M36)	132	36	27.3	19.9	35.7	27	20.5	13.9	28.3	12.1	8.5	17.3
		PI(M48)	132	36	27.3	19.9	35.7	26	19.7	13.3	27.5	12.0	8.4	17.2
rSBA-MenY	ACWY-TT	PI(M36)	399	370	92.7	89.7	95.1	353	88.5	84.9	91.4	674.9	557.6	816.8
		PI(M48)	400	358	89.5	86.1	92.3	343	85.8	81.9	89.0	545.0	440.7	673.9
	MenPS	PI(M36)	132	73	55.3	46.4	64.0	65	49.2	40.4	58.1	57.6	36.2	91.6
		PI(M48)	132	64	48.5	39.7	57.3	61	46.2	37.5	55.1	49.5	30.6	79.9

ACWY-TT = MenACWY-TT
MenPS = *Mencevax* ACWY
GMT = geometric mean titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre above the specified cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PI(M36) = Post-primary vaccination at Month 36
PI(M48) = Post-primary vaccination at Month 48.

- Safety results

None of the subjects reported SAEs that were related to study participation or were related to a concurrent GSK medication from the last visit of the primary vaccination study up to 48 months after the primary vaccination.

3. Discussion on clinical aspects

At 48 months after primary vaccination in study 109069 (MENACWY-TT-036), the percentages of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres ≥ 1:8 were 90.1%, 94.3%, 77.4% and 89.5% in the ACWY-TT group and 80.5%, 87.2%, 27.3% and 48.5% in the MenPS group, respectively. The results of these follow-up analyses demonstrate robust level of SBA immunity present in subjects 11-17 years of age who were primed with Nimenrix and retained rSBA immunogenicity at Y3 and Y4 for all four serogroups. The data from Y3 and 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.

Rapporteur's overall conclusion and recommendation

Clinical data from extension phase of MENACWY-TT-036 are considered supportive to persistence of rSBA response at Y3 and Y4 in adolescent subjects. An update of section 5.1 is accepted and will be fulfilled within the scope of variation -09.

☒ **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