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EMA/133615/2013
Committee for Medicinal Products for Human Use (CHMP)

Nimenrix

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

Procedure No. EMEA/H/C/000113/P46/0017

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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I. EXECUTIVE SUMMARY

Nimenrix is a quadrivalent meningococcal polysaccharide conjugate vaccine composed of Neisseria meningitides serogroups A, C, W-135 and Y conjugated to tetanus toxoid.
Nimenrix was authorised on 20th April 2012 for active immunisation of individuals from the age of 12 months and above against invasive meningococcal disease caused by Neisseria meningitides serogroups A, C, W-135 and Y.

The applicant submitted the final report for the paediatric Study MenACWY-TT-088 EXT081 M32 in accordance with Article 46 of Regulation (EC) No 1901/2006.
A short critical expert overview was also provided.

The applicant states 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.

A variation application consisting of the full relevant data package (i.e containing several studies to update the labelling with available persistence data) is expected to be submitted by the beginning of 2013.
An updated line listing of the concerned studies was provided by the applicant.

II. RECOMMENDATION[1]

No SmPC and PL changes are proposed.

III. INTRODUCTION

Nimenrix is a quadrivalent meningococcal polysaccharide conjugate vaccines composed of Neisseria meningitides serogroups A, C, W-135, Y conjugated to tetanus toxoid. Nimenrix was authorised on 20th April 2012 for active immunisation of individuals from the age of 12 months and above against invasive meningococcal disease cause by Neisseria meningitides group A, C, W-135 and Y.
The data has been submitted in accordance with Article 46.

The study MenACWY-TT-088 EXT081 M32 is a **follow-up study at 32 months** of the primary study MenACWY-TT-081. The primary phase study MenACWY-TT-081was submitted as part of the initial MAA for Nimenrix. Further follow-up of the subjects is planned up to 68 months following primary vaccination in MenACWY-TT-081 and a full report describing the persistence results or 32 through to 68 months after primary vaccination will be written when the results of the Month 68 persistence study are available.

IV. SCIENTIFIC DISCUSSION

IV.1 Clinical aspects

Study detailed title
A phase IIIb, open, multi-centre, controlled study to assess the long-term persistence of antibodies after a single dose of GlaxoSmithKline (GSK) Biologicals' meningococcal serogroup ACWY tetanus-toxoid conjugate vaccine (MenACWY-TT) versus one dose of Novartis' meningococcal serogroup C CRM197 conjugate vaccine (*Menjugate*®) administered in healthy subjects aged 2 through 10 years in study MENACWY-TT-081 PRI (111414)

and to evaluate the safety and immunogenicity of a booster dose of MenACWY-TT administered 68 months post-primary vaccination.

Note: This clinical study report presents the persistence **results at Month 32 after primary vaccination** in study MENACWY-TT-081 PRI (111414).

Study Centres: This study was conducted at 25 centres (8 centres in France and 17 centres in Germany).

Study period: Study initiation date: 03 January 2011. Study completion date: 03 May 2011
Data lock point (Date of database freeze): 04 July 2012

Indication: Vaccination of children 2 to 10 years of age against invasive disease caused by meningococcal serogroups A, C, W-135, and Y.

Treatment: The study consisted of two parallel groups based on the vaccination received:

- ACWY-TT group: subjects were vaccinated with MenACWY-TT in the primary vaccination study MENACWY-TT-081 PRI (111414).
- MenCCRM group: subjects were vaccinated with *Menjugate* in the primary vaccination study MENACWY-TT-081 PRI (111414).

Objectives:
Primary:
Immunogenicity
Persistence
At 32, 44, 56 and 68 months after primary vaccination with MenACWY-TT or *Menjugate*:

- To evaluate the persistence of meningococcal antibodies in terms of the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY titres ≥1:8.

Secondary:
Immunogenicity
Persistence:

- At 32, 44, 56 and 68 months after primary vaccination with MenACWY-TT or *Menjugate*:
  - to evaluate the persistence of meningococcal antibodies in terms of the percentage of subjects with rSBA- MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres ≥1:128 and geometric mean titres (GMTs).
  - To evaluate the immune response of MenACWY-TT or *Menjugate* in terms of the percentage of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135, hSBA-MenY titres ≥1:4, ≥1:8 and GMTs.

One month post-booster vaccination at Month 69 after primary vaccination:

- One month post-booster vaccination with MenACWY-TT:
  - to evaluate the immunogenicity of a booster vaccination in terms of the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres ≥1:8, ≥1:128 and GMTs.
  - to evaluate the immunogenicity of a booster vaccination in terms of the percentage of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135, hSBA-MenY titres ≥1:4, ≥1:8 and GMTs.
  - to evaluate the immunogenicity of a booster vaccination in terms of the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY vaccine response.

The vaccine response to rSBA-MenA, C, W-135 and Y is defined as one month post-vaccination rSBA antibody titres ≥1:32 for initially seronegative subjects (i.e. pre-vaccination rSBA antibody titres <1:8) and at least a 4-fold increase in rSBA antibody titres from pre to post-vaccination for initially seropositive subjects (i.e. pre-vaccination rSBA antibody titres ≥1:8).

  - to evaluate the immunogenicity of a booster vaccination in terms of the percentage of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135, hSBA-MenY vaccine response.

The vaccine response to hSBA-MenA, C, W-135 and Y is defined as one month post-vaccination hSBA antibody titres ≥1:8 for initially seronegative subjects (i.e. pre-vaccination hSBA antibody titres <1:4) and at least a 4-fold increase in hSBA antibody titres from pre to post-vaccination for initially seropositive subjects (i.e. pre-vaccination hSBA antibody titres ≥1:4).
Safety and reactogenicity

- To evaluate the safety and reactogenicity of MenACWY-TT after the booster vaccination with respect to:
    - local and general solicited symptoms during the 4-day period (Days 0-3) following vaccination.
    - unsolicited serious and non-serious adverse events and new onset of chronic illness (e.g. autoimmune disorders, asthma, type I diabetes and allergies) during the 31-day period (Days 0-30) following vaccination.

Study design: An open, phase IIIb, multi-centre study with two parallel groups.
Subjects continuing into study MENACWY-TT-088 EXT: 081 M32, 44, 56, 68 (113977) retained their study group assignment. Subjects in study MENACWY-TT-088 EXT: 081 M32, 44, 56, 68 (113977) are to participate in 4 study visits at Months 32, 44, 56, and 68 after the primary vaccination in study MENACWY-TT-081 PRI (111414) and at 30 days after the Month 68 visit. A blood sample will be drawn at each time-point. All eligible subjects will receive a single booster dose of MenACWY-TT at 68 months post-primary vaccination.

Study vaccine, dose, mode of administration, lot no.:
Vaccination schedule /site: MenACWY-TT vaccine was given intramuscularly in the deltoid or thigh area of the non-dominant side in study MENACWY-TT-081 PRI (111414). In the current study, a single booster dose of MenACWY-TT vaccine will be administered intramuscularly in the left deltoid to all subjects at Month 68 post-primary vaccination in study MENACWY-TT-081 PRI (111414).

Vaccine composition /dose /lot number: Single dose vaccination with MenACWY-TT vaccine in study MENACWY-TT-081 PRI (111414) and single dose vaccination with MenACWY-TT vaccine in the current study at Month 68. Details will be provided in the Month 68 annex report.

Reference vaccine /Comparator, dose and mode of administration, lot no.:
Vaccination schedule /site: *Menjugate* vaccine was given intramuscularly in the deltoid or thigh area of the non-dominant side in study MENACWY-TT-081 PRI (111414). In the current study, a single booster dose of MenACWY-TT vaccine will be administered intramuscularly in the left deltoid to all subjects at Month 68 post-primary vaccination in study MENACWY-TT-081 PRI (111414).

Vaccine composition /dose /lot number: Single dose vaccination with *Menjugate* vaccine in study MENACWY-TT-081 PRI (111414) and single dose vaccination with MenACWY-TT vaccine in the current study at Month 68. Details will be provided in the Month 68 annex report.

Study Population: Healthy males and females who were primed with MenACWY-TT or *Menjugate* in the primary vaccination study MENACWY-TT-081 PRI (111414), who completed an assent form (per investigator discretion), and whose parent(s)/Legally Acceptable Representatives (LAR[s]) gave written informed consent. No previous vaccination with a meningococcal polysaccharide or a meningococcal polysaccharide conjugate vaccine (including investigational vaccines) since the previous vaccination in the primary vaccination study MENACWY-TT-081 PRI (111414) were to have been administered. Subjects had to be without a history of meningococcal disease.

Duration of the study: The maximum duration of the study will be approximately three years per subject.

Primary Outcome/Efficacy Variable:
Persistence of antibodies in all subjects with respect to components of the investigational vaccine:
- rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY titres ≥1:8 at 32, 44, 56 and 68 months after the primary vaccination.

Secondary Outcome/Efficacy Variables:
Immunogenicity
Persistence of antibodies in all subjects with respect to components of the investigational vaccine (on secondary readouts):
- rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY titres ≥1:128 and GMTs at 32, 44, 56 and 68 months after the primary vaccination.
- hSBA-MenA, hSBA-MenC, hSBA-MenW-135, hSBA-MenY titres ≥1:4, ≥1:8 and GMTs in 50% of the subjects at 32, 44 and 56 months and in all subjects at 68 months after the primary vaccination.

Immunogenicity of booster vaccination in all subjects with respect to components of the investigational vaccine:

- rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY antibody titres ≥1:8, ≥1:128, GMTs and rSBA vaccine response one month post-booster vaccination at Month 69 after primary vaccination.
  The vaccine response to rSBA-MenA, C, W-135 and Y is defined as one month post-vaccination rSBA antibody titres ≥1:32 for initially seronegative subjects (i.e. pre-vaccination rSBA antibody titres <1:8) and at least a 4-fold increase in rSBA antibody titres from pre to post-vaccination for initially seropositive subjects (i.e. pre-vaccination rSBA antibody titres ≥1:8).

- hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY antibody titres ≥1:4, ≥1:8, GMTs and hSBA vaccine response one month post-booster vaccination at Month 69 after primary vaccination.
  The vaccine response to hSBA-MenA, C, W-135 and Y is defined as one month post-vaccination hSBA antibody titres ≥1:8 for initially seronegative subjects (i.e. pre-vaccination hSBA antibody titres <1:4) and at least a 4-fold increase in hSBA antibody titres from pre to post-vaccination for initially seropositive subjects (i.e. pre-vaccination hSBA antibody titres ≥1:4).

Reactogenicity and safety

Solicited local and general symptoms:

- Occurrence of each solicited local symptom during the 4-day period (Days 0-3) following the booster vaccination.
- Occurrence of each solicited general symptom during the 4-day period (Days 0-3) following the booster vaccination.

Unsolicited adverse events:

- Occurrence of unsolicited adverse events during the 31-day period (Days 0-30) following the booster vaccination.

Serious adverse events (SAEs):

- Occurrence of SAEs during the 31-day period (Days 0-30) following the booster vaccination.

Specific adverse events:

- Occurrence of new onset of chronic illness (e.g. autoimmune disorders, asthma, type I diabetes and allergies) during the 31-day period (Days 0-30) following the booster vaccination.

Statistical methods: The statistical analyses were performed using the SAS® software version 9.2 and Proc StatXact 8.1.

Analyses were performed as per the study Reporting and Analysis Plan (RAP). Only the statistical methods pertaining to the Month 32 persistence time-point are described.

Analysis of demographics/baseline characteristics:

- Demographic characteristics of each study cohort were tabulated: age at Month 32 and months since the primary vaccination (Month 0 for the ACWY-TT and MenCCRM groups in the primary vaccination study MENACWY-TT-081 PRI [111414]) at each persistence time-point, gender, and geographic ancestry.
- The mean age (at the persistence time-point (in years) [with the range and standard deviation]) as well as the proportion of males and females were calculated and presented by group.
- The distribution of subjects enrolled at Month 32 among the study sites was tabulated as a whole and per group and reason for not attending a visit at Month 32 among all subjects who participated in the primary vaccination study MENACWY-TT-081 PRI (111414) were summarized.

Analysis of persistence

For Month 32: The analysis of antibody persistence was based on the According to Protocol (ATP) cohort for antibody persistence at Month 32. If, for any vaccine group, the percentage of subjects who came back for the Month 32 follow-up with serological results excluded from the ATP cohort was higher than 5%, a second analysis based on the Total Vaccinated Cohort Month 32 was to be performed to complement the ATP analysis.

For each treatment group, at each blood sampling time-point, for each antigen assessed:

- Geometric mean titres (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 presented using reverse cumulative curves.

Analysis of safety

At the Month 32 persistence time-point, all reported SAEs considered related to study procedures, or a concomitant GSK drug or vaccine, or fatal SAEs were to be described in detail.

Synopsis Table 1: Study population (Total cohort at M32)		
Number of subjects	**ACWY-TT**	**MenCCRM**
Planned, N	150	50
Enrolled in study 088, N (Total Cohort at Month 32)	199	72
Completed Month 32, n (%)	199 (100)	72 (100)
Total Number Subjects Withdrawn at visit 1, n (%)	0 (0.0)	0 (0.0)
Withdrawn due to Adverse Events, n (%)	0 (0.0)	0 (0.0)
Withdrawn due to Lack of Efficacy, n (%)	Not Applicable	Not Applicable
Withdrawn for other reasons, n (%)	0 (0.0)	0 (0.0)
Demographics	**ACWY-TT**	**MenCCRM**
N (Total Cohort at Month 32)	199	72
Females:Males	103:96	34:38
Mean Age, years (SD)	8.4 (2.58)	8.1 (2.42)
White – Caucasian / European heritage, n (%)	169 (84.9)	61 (84.7)
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)		

Summary:
Immunogenicity: The analysis of antibody persistence was based on the ATP cohort for antibody persistence at Month 32. Since, for any vaccine group, the percentage of subjects who came back for the Month 32 follow-up with serological results excluded from the ATP cohort was not higher than 5%, a second analysis based on the Total cohort at Month 32 was not performed to complement the ATP analysis.

Note that since the rSBA serological testing at pre-vaccination and one month post-vaccination in study MENACWY-TT-081 PRI (11141) were performed at GSK laboratories, and whereas the rSBA testing at Month 32 post-vaccination were performed at Health Protection Agency (HPA) laboratories in the United Kingdom, these data are presented in separate tables and the antibody kinetics and decay from pre-vaccination and one month post-vaccination in study MENACWY-TT-081 PRI (11141) to the Month 32 time-point cannot be directly assessed.

Assessor's comment: The switch from GSK to HPA testing for rSBA was previously communicated during the MAA application. This change in methodology precludes direct assessment of the antibody kinetics and decay from pre-vaccination and one month post-vaccination to the month 32 time-point. Such a direct comparison of month 32 with later time points; namely the planned analyses at months 44, 56 and 68 after primary vaccination will be possible when further data is available from the ongoing study.

At Month 32 after primary vaccination,

- The percentage of subjects with rSBA-MenA titres ≥1:8 were 86.5% in the ACWY-TT group and 21.7% in the MenCCRM group.
- The percentage of subjects with rSBA-MenC titres ≥1:8 were 64.6% in the ACWY-TT group and 76.8% in the MenCCRM group.
- The percentage of subjects with rSBA-MenW-135 titres ≥1:8 were 77.2% in the ACWY-TT group and 7.2% in the MenCCRM group.
- The percentage of subjects with rSBA-MenY titres ≥1:8 were 81.3% in the ACWY-TT group and 14.5% in the MenCCRM group.

Synopsis Table 2: Percentage of subjects with GSK rSBA titres equal to or above the cut-off values of 1:8 and 1:128 and GMTs (ATP cohort for persistence at Month 32)

				≥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	148	63	42.6	34.5	51.0	54	36.5	28.7	44.8	27.3	18.7	39.7
		PI(M1)	191	191	100	98.1	100	191	100	98.1	100	6733.3	5927.0	7649.3
	MenCCRM	PRE	51	24	47.1	32.9	61.5	20	39.2	25.8	53.9	31.4	16.5	59.9
		PI(M1)	57	25	43.9	30.7	57.6	19	33.3	21.4	47.1	27.2	14.4	51.1
rSBA-MenC	ACWY-TT	PRE	173	78	45.1	37.5	52.8	42	24.3	18.1	31.4	20.9	15.7	27.9
		PI(M1)	189	189	100	98.1	100	186	98.4	95.4	99.7	2588.0	2124.5	3152.7
	MenCCRM	PRE	65	31	47.7	35.1	60.5	13	20.0	11.1	31.8	20.9	12.8	34.1
		PI(M1)	67	67	100	94.6	100	67	100	94.6	100	5135.3	3436.5	7674.1
rSBA-MenW-135	ACWY-TT	PRE	179	138	77.1	70.2	83.0	93	52.0	44.4	59.5	76.3	58.3	99.7
		PI(M1)	192	192	100	98.1	100	191	99.5	97.1	100	8959.1	7828.9	10252.5
	MenCCRM	PRE	64	51	79.7	67.8	88.7	31	48.4	35.8	61.3	75.1	47.9	117.6
		PI(M1)	65	52	80.0	68.2	88.9	30	46.2	33.7	59.0	77.9	49.4	122.9
rSBA-MenY	ACWY-TT	PRE	184	159	86.4	80.6	91.0	122	66.3	59.0	73.1	155.3	120.1	200.7
		PI(M1)	191	191	100	98.1	100	191	100	98.1	100	8543.9	7405.0	9858.1
	MenCCRM	PRE	61	47	77.0	64.5	86.8	30	49.2	36.1	62.3	70.2	43.9	112.3
		PI(M1)	65	51	78.5	66.5	87.7	34	52.3	39.5	64.9	86.5	54.5	137.3

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)
GMT = geometric mean titre calculated on all subjects
N = number of subjects with results available
n/% = number/percentage of subjects with titre equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Day 0, pre-primary vaccination
PI(M1) = 1 month post-primary vaccination with meningococcal vaccine

Synopsis Table 3: Percentage of subjects with HPA rsba titres equal to or above the cut-off values of 1:8 and 1:128 and GMTs (ATP cohort for persistence at Month 32)

				≥ 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)	193	167	86.5	80.9	91.0	140	72.5	65.7	78.7	196.3	144.1	267.2
	MenCCRM	PI(M32)	69	15	21.7	12.7	33.3	9	13.0	6.1	23.3	8.0	5.5	11.7
rSBA-MenC	ACWY-TT	PI(M32)	192	124	64.6	57.4	71.3	69	35.9	29.2	43.2	34.8	26.0	46.4
	MenCCRM	PI(M32)	69	53	76.8	65.1	86.1	35	50.7	38.4	63.0	86.5	47.3	158.1
rSBA-MenW-135	ACWY-TT	PI(M32)	193	149	77.2	70.6	82.9	136	70.5	63.5	76.8	213.9	149.3	306.6
	MenCCRM	PI(M32)	69	5	7.2	2.4	16.1	5	7.2	2.4	16.1	5.6	4.2	7.6
rSBA-MenY	ACWY-TT	PI(M32)	193	157	81.3	75.1	86.6	145	75.1	68.4	81.1	227.4	164.8	313.7
	MenCCRM	PI(M32)	69	10	14.5	7.2	25.0	8	11.6	5.1	21.6	7.2	5.0	10.4

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)
GMT = geometric mean titre calculated on all subjects
N = number of subjects with results available
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(M32) = Month 32, 32 months post-primary vaccination

Of note and previously communicated during the MAA application, 32 months after vaccination in study MenACWY-TT-081, all samples collected were tested using rSBA assays performed at the Health Protection Agency (HPA) and samples from a subset of 50% of the subjects were tested with GSK hSBA assay (which corresponds to 86 to 91 and 23 to 34 subjects for whom hSBA results are available across serogroups for ACWY-TT and MenCCRM groups respectively.

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

				≥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)	90	24	26.7	17.9	37.0	23	25.6	16.9	35.8	4.6	3.3	6.3
	MenCCRM	PI(M32)	34	5	14.7	5.0	31.1	5	14.7	5.0	31.1	2.7	2.1	3.4
hSBA-MenC	ACWY-TT	PI(M32)	90	86	95.6	89.0	98.8	86	95.6	89.0	98.8	75.9	53.4	107.9
	MenCCRM	PI(M32)	33	30	90.9	75.7	98.1	30	90.9	75.7	98.1	82.2	34.6	195.8
hSBA-MenW-135	ACWY-TT	PI(M32)	86	73	84.9	75.5	91.7	73	84.9	75.5	91.7	69.9	48.2	101.5
	MenCCRM	PI(M32)	23	4	17.4	5.0	38.8	4	17.4	5.0	38.8	3.8	2.0	7.1
hSBA-MenY	ACWY-TT	PI(M32)	91	74	81.3	71.8	88.7	74	81.3	71.8	88.7	79.2	52.5	119.3
	MenCCRM	PI(M32)	28	13	46.4	27.5	66.1	13	46.4	27.5	66.1	15.1	6.3	36.5

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)
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with results available
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(M32) = Month 32, 32 months post-primary vaccination

One finding of the vaccination study MenACWY-TT-081 was that the GSK rSBA MenC-GMT elicited by Menjugate was higher than the one observed for the MenACWY-TT vaccine (5292.6 vs. 2794.8; 95% CI of the GMT ratio excluded the value of 1). It has been concluded that the clinical relevance of this finding is limited given that GMTs were high in both groups and no statistically significant difference was observed between the two groups in terms of percentage of subjects with rSBA titres titres ≥ 8 and ≥ 128 (the percentage of subjects with GSK rSBA-MenC titre ≥128 was 99.3% in the ACWY-TT group versus 100% in the MenCCRM group).

Assessor's comment: What is noted in the table above is the low percentage of the ACWY-TT group with titres equal to or above the cut-off values of 1:4 and 1:8 for hSBA-MenA GSK assay.
However the results for rSBA-MenA (synopsis Table 3) show a high percentage of subjects with titres equal to or above the cut-off values of 1:4 and 1:8 and a clear difference between the two vaccination groups. It is also noted that larger numbers contributed to the rSBA tests performed by HPA.
The rapid waning of serum bactericidal antibody titres against MenA when using human complement in the assay is already highlighted in the SmPC.

Safety:
No analysis of safety was performed in this study at the Month 32 persistence time-point. All reported SAEs considered related to study procedures were to be described in detail. SAEs related to a concomitant GSK drug or vaccine were to be collected and reported to regulatory authorities.
No SAEs related to study participation or related to concurrent GSK medication were reported from the end of the six-month Extended Safety Follow-up period following vaccination in study MENACWY-TT-081 PRI (11141) until the Month 32 persistence time-point.

MAH Conclusions:

- The percentage of subjects with rSBA-MenA titres ≥1:8 at Month 32 were 86.5% in the ACWYTT group and 21.7% in the MenCCRM group.

- The percentage of subjects with rSBA-MenC titres ≥1:8 at Month 32 were 64.6% in the ACWY-TT group and 76.8% in the MenCCRM group.
- The percentage of subjects with rSBA-MenW-135 titres ≥1:8 at Month 32 were 77.2% in the ACWY-TT group and 7.2% in the MenCCRM group.
- The percentage of subjects with rSBA-MenY titres ≥1:8 at Month 32 were 81.3% in the ACWYTT group and 14.5% in the MenCCRM group.
- 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 six-month Extended Safety Follow-up period following vaccination in study MENACWY-TT-081 PRI (111414) until the Month 32 persistence time-point.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➢ Overall conclusion

For P46 017 the data consisted of Month 32 follow-up data on immunogenicity and safety from Study MenACWY-TT-088 EXT081.

In view of the changes in rSBA testing from GSK to HPA, it is not possible to assess the antibody kinetics and decay from pre-vaccination and one month post-vaccination to the month 32 time-point. Such a direct comparison of month 32 with later time points; namely the planned analyses at months 44, 56 and 68 after primary vaccination will be possible when further data is available from the ongoing study.

No SAEs occurred during this follow-up period.

The MAH is planning a variation application consisting of the full relevant data package (i.e containing several studies to update the labelling with available persistence data) and expects to submit this by the beginning of 2013.

No SmPC changes are required following from this article 46 procedure.

➢ Recommendation

No further action required.