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/P46/0038

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.

The company has submitted the report for paediatric study [MenACWY-TT-020 EXT015 Year 5] in accordance with Article 46 of Regulation (EC) No 1901/2006. This report presents the persistence results at 5 years after vaccination.

The company 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. SmPC and PL changes arising from the currently submitted data are not proposed (the company has submitted a type II variation (EMEA/H/C/2226/II/009, currently under review) to update the SmPC with persistence data up to 4 years after primary vaccination).

2. Recommendation

Regulatory action is not required.

3. Introduction

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.

The company now submits the report for paediatric study MenACWY-TT-020 EXT015 Year 5 in accordance with Article 46 of Regulation (EC) No 1901/2006. This report presents the persistence results at 5 years after vaccination.

The overall study has consisted of two phases: the vaccination phase study [MenACWY-TT-015] and the long-term persistence phase (1 to 5 years) after vaccination studies [MenACWY-TT-016 EXT: 015 Y1]; [MenACWY-TT-017 EXT: 015 Y2]; [MenACWY-TT-018 EXT: 015 Y3]; [MenACWY-TT-019 EXT: 015 Y4] and [MenACWY-TT-020 EXT: 015 Y5].

The primary phase study MenACWY-TT-015 and 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. Years 3 and 4 follow-up data in studies MenACWY-TT-018 and MenACWY-TT-019 have been previously submitted and assessed under Article 46. The company has submitted a type II variation (EMEA/H/C/2226/II/009, currently under review) to update the SmPC with persistence data up to 4 years after primary vaccination

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

4. Scientific Discussion

Study: [MenACWY-TT-020 EXT: 015 Y5]

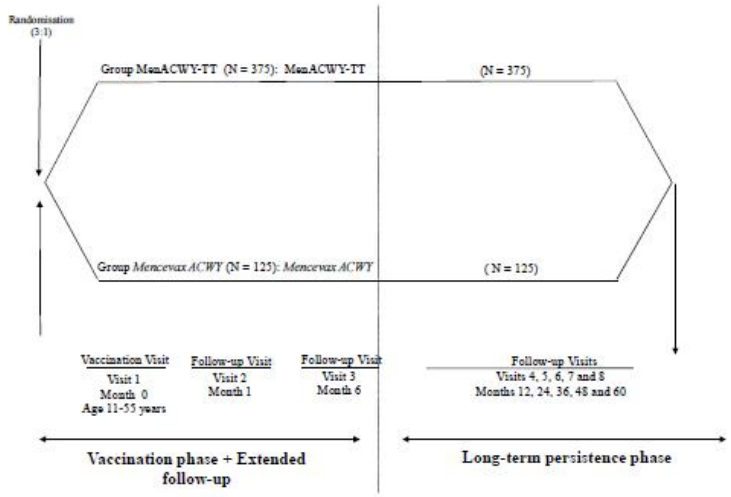
EudraCT number: 2012-002722-75

Study title: A phase IIb, open, randomised, controlled primary vaccination study to evaluate the non-inferiority and the persistence of the immune response of GSK Biologicals' meningococcal serogroup ACWY conjugate vaccine (Nimenrix) given intramuscularly versus Mencevax ACWY given subcutaneously to healthy subjects aged 11 to 55 years of age.

Assessor comment: the study has been described in previous assessment reports: a brief outline is given here.

The study design is shown in the following figures:

5.1. Study design



- **Experimental design:** Phase IIb, open, randomised [3:1], controlled, multicentre study with two parallel groups.

  This study was conducted in two stages:

  - Vaccination stage (primary phase),
  - Extended persistence follow-up (long-term persistence phase).
- **Treatment groups:**
  - Group MenACWY-TT: Subjects who received one intramuscular (IM) dose of MenACWY-TT during the vaccination phase (107386 [MenACWY-TT-015]),
  - Group Mencevax ACWY: Subjects who received one subcutaneous (SC) dose of *Mencevax ACWY* during the vaccination phase (107386 [MenACWY-TT-015]).
- **Treatment allocation:** Subjects were randomized (3:1) using Central Randomization call-in System on internet (SBIR) in the vaccination phase of the study 107386 (MenACWY-TT-015). They were not further randomized in the persistence studies but remained in the same groups.
- **Blinding:** open.
- **Active Control:** *Mencevax ACWY*.

- **Blood sampling:** Blood samples were collected from the subjects in both groups at each yearly persistence time point, i.e., at one, two, three, four and five years after vaccination (Visits 4, 5, 6, 7 and 8/ Months 12, 24, 36, 48 and 60 post-vaccination).
- **Type of study:** Self-contained. However, the database was split into 6 stages: stage 1: up to six months post vaccination; then each subsequent five stages corresponding to one subsequent year post vaccination, up to five years post vaccination.
- **Data collection:** Remote Data Entry (RDE).
- **Duration of the study:** For each subject, the study duration was approximately five years.

Study [MenACWY-TT-020 EXT: 015 Y5] was conducted in the Saudi Arabia and the Philippines. This study evaluated the persistence of the immune response and the occurrence of serious adverse events related to vaccination and events related to lack of vaccine efficacy up to 5 years after vaccination with Nimenrix or the Mencevax ACWY control vaccine in study [MenACWY-TT-015].

The primary end-point was related to the vaccination phase and has been previously assessed

(Secondary) endpoints:

- Immunogenicity: One, two, three, four and five years after vaccination (for evaluation of the persistence), in all evaluable subjects: rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres ≥1:8 and titres.
- Reactogenicity and safety: occurrence of serious adverse events (including meningococcal diseases) related to vaccination and any event related to lack of vaccine efficacy from the last visit of the vaccination phase up to the last visit of the long-term persistence phase (5 years after vaccination).

Study initiation date: 03 January 2012

Study completion date: 16 February 2013

Data lock point (Date of database freeze): 22 May 2013

Due to a delay in the annual approval from the Institutional Review Board for the Year 5 persistence time point of the current study, all 333 subjects enrolled at the Philippine study sites attended the Year 5 visit outside the adapted intervals between vaccination at Visit 1 in the primary study [MenACWY-TT-015] and the Year 5 blood sampling time point in the current study. As a result, all 333 Philippine subjects were eliminated from the 'according to protocol' analysis at Year 5 because of non-compliance with the blood sampling schedule.

Assessor comment: 70 subjects remained 'according to protocol' whilst 333 subjects were excluded as a result of delay in approval. As a result of this mishap, the results of this 5-year follow-up study are much compromised and so only a brief description of results is presented in this assessment.

The company has sought to retrieve the situation by describing two cohorts, 'according to protocol' cohort and 'Total Cohort Year 5', as described immediately below:

Two cohorts were defined for the purpose of analysis of antibody persistence.

The **Total Cohort Year 5** included all vaccinated subjects in the vaccination phase (study [MenACWY-TT-015]) who came back for the Year 5 follow-up. For the analysis of persistence, this includes all vaccinated subjects for whom data concerning persistence endpoint measures were available.

The **'according-to-protocol' cohort** for persistence Year 5 included all evaluable subjects:

- who received the vaccine during the vaccination phase;
- who had not received a previous dose of meningococcal serogroup A, C, W-135 or Y vaccines except the study vaccine before Year 5;
- who had available assay results for at least one tested antigen at the Year 5 time point.

Results

Clinical efficacy

The demographic characteristics of the 'according to protocol' cohort for persistence Year 5 are presented in the following table:

Table 6 Summary of demographic characteristics (ATP cohort for persistence Year 5)

		ACWY-TT N = 51		MenPS N = 19		Total N = 70	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Age (years) at Year 5	Mean	22.67	-	22.16	-	22.53	-
	SD	5.82	-	6.59	-	5.99	-
	Median	21.00	-	20.00	-	21.00	-
	Minimum	16.00	-	16.00	-	16.00	-
	Maximum	36.00	-	39.00	-	39.00	-
Age stratum (years)	11-17	28	54.9	13	68.4	41	58.6
	18-55	23	45.1	6	31.6	29	41.4
Gender	Female	17	33.3	8	42.1	25	35.7
	Male	34	66.7	11	57.9	45	64.3
Geographic Ancestry	African heritage/African American	0	0.0	0	0.0	0	0.0
	American Indian or Alaskan Native	0	0.0	0	0.0	0	0.0
	Asian - Central/South Asian heritage	0	0.0	0	0.0	0	0.0
	Asian - East Asian heritage	0	0.0	0	0.0	0	0.0
	Asian - Japanese heritage	0	0.0	0	0.0	0	0.0
	Asian - South East Asian heritage	0	0.0	0	0.0	0	0.0
	Native Hawaiian or Other Pacific Islander	0	0.0	0	0.0	0	0.0
	White - Arabic / North African heritage	51	100	19	100	70	100
	White - Caucasian / European heritage	0	0.0	0	0.0	0	0.0
	Other	0	0.0	0	0.0	0	0.0

ACWY-TT = Subjects who have received MenACWY-TT in the MenACWY-TT-015 (107386) study
MenPS = Subjects who have received *Mencevax* ACWY in the MenACWY-TT-015 (107386) study
11-17 = subjects below 18 years of age at the time of vaccination
18-55 = subjects of 18 years of age and above at the time of vaccination
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Based on the 'according to protocol' cohort for persistence Year 5 analysis, the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres ≥1:8 was 84.3%, 72.5%, 86.3% and 92.2%, respectively, in the ACWY-TT group and 57.9%, 38.9%, 31.6% and 63.2%, respectively, in the MenPS group.

The demographic characteristics of the Total Cohort Year 5 are presented in the following table:

Table 7 Summary of demographic characteristics (Total Cohort Year 5)

		ACWY-TT N = 299		MenPS N = 105		Total N = 404	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Age (years) at Year 5	Mean	23.29	-	23.55	-	23.36	-
	SD	7.70	-	8.10	-	7.80	-
	Median	20.00	-	20.00	-	20.00	-
	Minimum	16.00	-	16.00	-	16.00	-
	Maximum	58.00	-	51.00	-	58.00	-
Age stratum (years)	11-17	208	69.6	76	72.4	284	70.3
	18-55	91	30.4	29	27.6	120	29.7
Gender	Female	136	45.5	52	49.5	188	46.5
	Male	163	54.5	53	50.5	216	53.5
Geographic Ancestry	African heritage/African American	0	0.0	0	0.0	0	0.0
	American Indian or Alaskan Native	0	0.0	0	0.0	0	0.0
	Asian - Central/South Asian heritage	0	0.0	0	0.0	0	0.0
	Asian - East Asian heritage	0	0.0	0	0.0	0	0.0
	Asian - Japanese heritage	0	0.0	0	0.0	0	0.0
	Asian - South East Asian heritage	247	82.6	86	81.9	333	82.4
	Native Hawaiian or Other Pacific Islander	0	0.0	0	0.0	0	0.0
	White - Arabic / North African heritage	52	17.4	19	18.1	71	17.6
	White - Caucasian / European heritage	0	0.0	0	0.0	0	0.0
	Other	0	0.0	0	0.0	0	0.0

ACWY-TT = Subjects who have received MenACWY-TT in the MenACWY-TT-015 (107386) study
MenPS = Subjects who have received *Mencevax* ACWY in the MenACWY-TT-015 (107386) study
11-17 = subjects below 18 years of age at the time of vaccination
18-55 = subjects of 18 years of age and above at the time of vaccination
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Based on the Total Cohort Year 5 analysis, the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres ≥1:8 was 90.0%, 79.3%, 71.6% and 84.3%, respectively, in the ACWY-TT group and 74.3%, 71.2%, 24.8% and 44.8%, respectively, in the MenPS group.

Assessor comment: the results, as presented, would not appear to give rise to any particular concerns regarding the current product. The company had already decided to undergo a variation procedure (EMEA/H/C/2226/II/009, currently under review) based on year 4 data. The company will be able to provide further information at the 10-year check on subjects. The overall value of the study, therefore, will not be lost.

Clinical safety

No serious adverse events related to vaccination or events related to lack of efficacy have been reported since vaccination in study [MenACWY-TT-015] up to five years post-vaccination.

Since the Year 4 persistence visit, six pregnancies were reported which all resulted in birth of a live infant with no apparent congenital anomalies.

Assessor comment: no additional comment.

5. Rapporteur's Overall Conclusion and Recommendation

Overall conclusion

It is not possible to provide substantive comment on the clinical efficacy results because 333 subjects (out of 405) had not followed the study protocol at the time of the year 5 check. The company had already decided to undergo a variation procedure (EMEA/H/C/2226/II/009, currently under review) based on year 4 data. The company will be able to provide further information at the 10-year check on subjects. The overall value of the study, therefore, will not be lost.

The results on clinical safety do not give rise to any particular concerns.

Recommendation

The Rapporteur concludes that the benefit / risk for Nimenrix is unchanged by data submitted in the current report and that there is no consequential need for regulatory action.