EMA/286542/2024
Committee for Medicinal Products for Human Use (CHMP)

Type II variation assessment report

Procedure No. EMEA/H/C/002226/II/0135

Invented name: Nimenrix

Common name: Meningococcal group A, C, W135 and Y conjugate vaccine

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	13 May 2024	13 May 2024
☐	CHMP Rapporteur Assessment Report	17 Jun 2024	17 Jun 2024
☐	CHMP members comments	01 Jul 2024	01 Jul 2024
☐	Updated CHMP Rapporteur Assessment Report	04 Jul 2024	04 Jul 2024
☐	Start of written procedure	09 Jul 2024	09 Jul 2024
☒	Opinion	11 Jul 2024	11 Jul 2024

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Europe MA EEIG submitted to the European Medicines Agency on 22 April 2024 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Update of section 5.1 of the SmPC in order to update immunogenicity response information based on results from Study C0921062 and following EMEA/H/C/002226/P46/057 procedure. Study C0921062 is a Phase 3b, open-label, with a single-arm design study, to evaluate the safety and immunogenicity of a single dose of Nimenrix in infants at 3 months of age, followed by a booster dose at 12 months of age. In addition, the MAH took the opportunity to implement editorial changes in the SmPC.

The requested variation proposed amendments to the Summary of Product Characteristics.

2. Overall conclusion and impact on the benefit/risk balance

This type II variation application concerns an update of SmPC Section 5.1 of the Nimenrix (MenACWY-TT) to add information regarding the immune response induced by 2 doses of Nimenrix administered at 3 and 12 months of age. This update was requested by the EMA/CHMP as part of the EU Article 46 procedure for Study C0921062 (Procedure Number EMA/H/C/002226/P46/057). The CSR for this study was submitted on 30 Nov 2023, with the Article 46 procedure fulfilled on 22 Feb 2024.

Nimenrix is a quadrivalent conjugate vaccine for the prevention of invasive infections with N. meningitidis serogroups A, C, W-135, and Y using TT as the carrier. Nimenrix has been licensed for use in the EU since April 2012 for individuals 12 months of age and above and since December 2016 the indicated age was lowered to 6 weeks of age and above. Current posology allows for 2 doses of Nimenrix before 6 months of age, where the first dose is administered from 6 weeks onwards with a second dose at least 2 months later, with a booster at 12 months; and in infants from 6 months of age, a single dose at 6 months, with a booster dose at 12 months.

Nimenrix was evaluated in the Phase 3, single-arm, open-label Study C0921062, with the purpose of describing safety and immunogenicity of a single dose of Nimenrix in infants at 3 months of age, followed by a booster dose at 12 months of age.

The primary immunogenicity objective was to describe the immune response induced by 2 doses of Nimenrix administered at 3 and 12 months of age as expressed by seroprotection (proportions achieving an rSBA titer $\geq$1:8) and rSBA GMTs for each of the MenA, MenC, MenW-135, and MenY serogroups. hSBA measurement was a secondary endpoint, however, due to insufficient blood volume collection rSBA measurements were prioritised. No data on hSBA is therefore included in Section 5.1 of the SmPC.

The immunogenicity data from Study C0921062 indicate that Nimenrix given at 3 and 12 months of age provides protective immune responses as measured by rSBA titers for a high proportion of participants at 1 month after Vaccination 1, administered at 3 months of age, and for all participants at 1 month after Vaccination 2, administered at 12 months of age, across all 4 serogroups. In addition, the results showed that Nimenrix given to infants 3 to 12 months of age was well tolerated and consistent with the established safety profile of Nimenrix in this population.

The data from Study C0921062 was considered of interest to the prescriber for inclusion in Section 5.1, but insufficient to warrant any change to the current posology (Section 4.2 in the SmPC).

The benefit-risk balance of Nimenrix, remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation approved		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Update of section 5.1 of the SmPC in order to update immunogenicity response information based on results from Study C0921062 and following EMEA/H/C/002226/P46/057 procedure. Study C0921062 is a Phase 3b, open-label, with a single-arm design study, to evaluate the safety and immunogenicity of a single dose of Nimenrix in infants at 3 months of age, followed by a booster dose at 12 months of age. In addition, the MAH took the opportunity to implement editorial changes in the SmPC

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I are recommended.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Nimenrix EMEA/H/C/002226/II/0135'

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Nimenrix is a quadrivalent conjugate vaccine for the prevention of invasive infections with N. meningitidis serogroups A, C, W-135, and Y using TT as the carrier. Nimenrix has been licensed for use in the EU since April 2012 for individuals 12 months of age and above and since December 2016 the indicated age was lowered to 6 weeks of age and above.

Nimenrix was evaluated in Study C0921062 with the purpose of describing the safety and immunogenicity of a single dose of Nimenrix in infants at 3 months of age, followed by a booster dose at 12 months of age. Current posology allows for 2 doses of Nimenrix in infants from 6-weeks to 6 months of age with an interval of 2 months between doses. This should be followed by a booster dose at 12 months. Study C0921062 provides immunogenicity and safety data for a single dose in healthy infants <6 months of age, followed by the booster at 12 months.

According to the SmPC guideline (A Guideline on Summary of Product Characteristics, 2009), section 5.1, Paediatric Population: "*Information should be updated when new relevant information becomes available*". This type II variation application concerns an update of section 5.1 of the SmPC to add information regarding the immune response induced by 2 doses of Nimenrix administered at 3 and 12 months of age. The update of the SmPC was requested by the EMA/CHMP as part of the EU Article 46 procedure for Study C0921062 (Procedure Number EMEA/H/C/002226/P46/057). The data was considered to be of interest to prescribers especially in instances where a child has, for some reason, not received the second dose two months after the first according to the posology. However, the data was considered insufficient to warrant any change to the current posology for the age group 6 weeks to <6 months in section 4.2 of the SmPC.

6. Clinical Efficacy aspects

6.1. Methods – analysis of data submitted

The purpose of the Phase 3b, multicenter, open-label study, with a single-arm design, was to evaluate the safety and immunogenicity of a single dose of Nimenrix in infants at 3 months of age, followed by a booster dose at 12 months of age. A total of 149 healthy infants 3 months of age ($\geq$76 to $\leq$104 days) were enrolled to a single vaccine group to receive Nimenrix (MenACWY-TT). All participants had not received previous vaccination with any meningococcal vaccine containing groups A, C, W or Y and had been born after >36 weeks of gestation. Children with immunosuppression were excluded from the study.

On Day 1 (Visit 1), participants were assessed for eligibility (including medical history and meningococcal vaccine history). If eligible, participants had their blood drawn for immunogenicity assessments and received the first dose of Nimenrix. Participants received a booster dose of Nimenrix at 12 months of age (Visit 3). Participants had their blood drawn prior to vaccination at Visit 1 (Vaccination 1) and Visit 3 (Vaccination 2) and 1 month after each vaccination at Visit 2 and Visit 4. A 0.5-mL dose of Nimenrix was administered intramuscularly in the infant's anterolateral region of the left thigh by a qualified site staff member. E-diaries were used to collect local reaction and systemic event data for 7 days after each vaccination. AEs were collected through 1 month after each vaccination. In addition, SAEs and NDCMCs were collected throughout the study from Visit 1 through Visit 4 (1 month after Vaccination 2).

Each participant participated in the study for approx. 10 months.

The primary immunogenicity objective was to describe the immune response for *N meningitidis* serogroups A, C, W-135, and Y induced by 2 doses of Nimenrix administered at 3 and 12 months of age as measured by:

- The percentage of participants with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY titers ≥1:8 for each serogroup at baseline, at 1 month after Vaccination 1, before Vaccination 2 and at 1 month after Vaccination 2 with Nimenrix.
- rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY GMTs for each serogroup at baseline, at 1 month after Vaccination 1, before Vaccination 2 and at 1 month after Vaccination 2 with Nimenrix.

Analysis of hSBA titres and GMT formed secondary endpoints.

The study sample size was not based on any hypothesis testing criteria. All statistical analyses of immunogenicity and safety were descriptive. The evaluable immunogenicity population was the primary immunogenicity population.

Blood draw visits before Vaccination 1 and 1 month after Vaccination 1, were prone to limited blood volumes obtained in these young infants aged 3 and 4 months, respectively. As a result, serum volumes available for hSBAs at these timepoints were limited.

6.2. Results

At 1 month after Vaccination 1, 82.3% to 91.1% of participants achieved rSBA titers ≥1:8 across the 4 serogroups compared to the baseline (0.0% to 7.8%). Prior to Vaccination 2, the proportion of participants with rSBA titers ≥1:8 ranged from 33.6% to 67.2% across the 4 serogroups. At 1 month after Vaccination 2, all participants (100%) achieved rSBA titers ≥1:8 across all 4 serogroups (Table 1).

Table 1. Number (%) of Participants With rSBA Titer ⩾1:8 at Each Visit – Post-Dose 2 Evaluable Immunogenicity Population

			Vaccine Group			
			Nimenrix			
Serogroup	Time Point	Titer	N[a]	n[b]	%	(95% CI[c])
MenA	Before Vaccination 1	≥1:8	128	0	0.0	(0.0, 2.8)
	1 Month after Vaccination 1	≥1:8	124	102	82.3	(74.4, 88.5)
	Before Vaccination 2	≥1:8	125	42	33.6	(25.4, 42.6)
	1 Month after Vaccination 2	≥1:8	128	128	100.0	(97.2, 100.0)
MenC	Before Vaccination 1	≥1:8	128	6	4.7	(1.7, 9.9)
	1 Month after Vaccination 1	≥1:8	124	113	91.1	(84.7, 95.5)
	Before Vaccination 2	≥1:8	125	81	64.8	(55.8, 73.1)
	1 Month after Vaccination 2	≥1:8	128	128	100.0	(97.2, 100.0)
MenW-135	Before Vaccination 1	≥1:8	128	1	0.8	(0.0, 4.3)
	1 Month after Vaccination 1	≥1:8	124	111	89.5	(82.7, 94.3)
	Before Vaccination 2	≥1:8	125	84	67.2	(58.2, 75.3)
	1 Month after Vaccination 2	≥1:8	128	128	100.0	(97.2, 100.0)
MenY	Before Vaccination 1	≥1:8	128	10	7.8	(3.8, 13.9)
	1 Month after Vaccination 1	≥1:8	124	112	90.3	(83.7, 94.9)
	Before Vaccination 2	≥1:8	125	83	66.4	(57.4, 74.6)
	1 Month after Vaccination 2	≥1:8	128	128	100.0	(97.2, 100.0)

Source: Study C0921062 CSR Table 9.
Abbreviations: rSBA = serum bactericidal assay using rabbit complement; MenA, MenC, MenW-135, and MenY = Neisseria meningitidis group A, group C, group W-135, and group Y.
a. N = number of participants with valid and determinate rSBA titers for the specified serogroup at the given time point. These values are used as the denominators for the percentage calculations.
b. n = Number of participants with observed rSBA titer for the specified serogroup at the given time point.

rSBA GMTs increased after Vaccination 1: ranging from 54.7 to 202.4 at 1 month after Vaccination 1. Prior to Vaccination 2, rSBA GMTs were higher than baseline ranging from 9.9 to 24.5 across the 4 serogroups. At 1 month after Vaccination 2, rSBA GMTs further increased, ranging from 1299.5 to 2714.1 (Table 2).

Table 2. rSBA GMTs at Each Visit – Post-Dose 2 Evaluable Immunogenicity Population

			Vaccine Group Nimenrix	
Serogroup	**Time Point**	**n[a]**	**GMT[b]**	**(95% CI[c])**
MenA	Before Vaccination 1	128	4.0	(4.0, 4.0)
	1 Month after Vaccination 1	124	54.7	(41.1, 72.9)
	Before Vaccination 2	125	9.9	(7.6, 13.0)
	1 Month after Vaccination 2	128	1818.0	(1497.8, 2206.6)
MenC	Before Vaccination 1	128	4.4	(4.0, 4.7)
	1 Month after Vaccination 1	124	107.6	(81.3, 142.5)
	Before Vaccination 2	125	21.8	(16.1, 29.5)
	1 Month after Vaccination 2	128	1299.5	(1052.3, 1604.9)
MenW-135	Before Vaccination 1	128	4.1	(3.9, 4.3)
	1 Month after Vaccination 1	124	202.4	(149.6, 274.0)
	Before Vaccination 2	125	21.7	(16.3, 28.9)
	1 Month after Vaccination 2	128	2714.1	(2233.0, 3298.8)
MenY	Before Vaccination 1	128	5.0	(4.3, 5.8)
	1 Month after Vaccination 1	124	187.2	(141.6, 247.5)
	Before Vaccination 2	125	24.5	(18.0, 33.4)
	1 Month after Vaccination 2	128	1667.1	(1393.9, 1993.8)

Abbreviations: GMT = geometric mean titer; rSBA = serum bactericidal assay using rabbit complement; LLOQ = lower limit of quantitation; MenA, MenC, MenW-135, and MenY = *Neisseria meningitidis* group A, group C, group W-135, and group Y .
Note: LLOQ = 1:8 for all MenA, MenC, MenW-135, and MenY serogroups. Titers below the LLOQ are set to 0.5 × LLOQ for analysis.
a. n = Number of participants with valid and determinate rSBA titers for the specified serogroup at the given time point.
b. GMTs are calculated using all participants with valid and determinate rSBA titers at the given time point.
c. CIs are obtained by exponentiating the limits of CIs for the mean logarithm of the rSBA titers (based on the Student t distribution).
PFIZER CONFIDENTIAL SDTM Creation: 16MAY2023 (16:11) Source Data: adva Table Generation: 07JUN2023 (13:30)
Output File: ./nda1 cdisc/C0921062 SERO/adva s001 rsba gmt pd2eval

It is noted that the GMTs of higher values have been rounded to the nearest whole number in the table in Section 5.1 in the SmPC. The table (currently Table 3) in Section 5.1 of SmPC does not define the study population, however, this is consistent with the other tables in the SmPC.

The data for hSBA was not included in the SmPC since a substantial proportion of participants did not contribute to the immunogenicity evaluation for MenW-135 and MenY hSBA before Vaccination 1 and at 1 month after Vaccination 1, due to indeterminate testing results, quantity and rSBA testing being prioritised over hSBA testing as this was the primary objective.

6.3. Discussion

The data from Study C0921062 based on rSBA responses show that Nimenrix given to infants at 3 and 12 months of age was well tolerated which was consistent with the established safety profile of Nimenrix in this population. The overall immunogenicity data from the study indicated that a high proportion of participants reached levels of seroprotection across the 4 serogroups following one dose of Nimenrix at 3 months of age. The GMT (rSBA) after a single vaccination in this study population are substantially lower than after two doses in infants 6-12 weeks of age described in the SmPC section 5.1 which involved a larger sample size. This is particularly evident for MenW-135 and MenY even though the frequency of participants achieving $\geq$1:8 for rSBA was >82% for all groups. A booster dose at 12 months of age provided anamnestic responses with all participants reaching levels of seroprotection (rSBA titre >1:8) after boosting, for all 4 serogroups.

As part of the EU Article 46 procedure for Study C0921062 (Procedure Number EMA/H/C/002226/P46/057), an update of Section 5.1 of the SmPC to include the data regarding the

immune response induced by 2 doses of Nimenrix administered at 3 and 12 months of age is proposed. This is supported. Prescribers are then informed on the potential for protection, should, for any reason, a single dose have been administered to infants aged 6 weeks to < 6 months. The data also emphasise the importance of the booster dose at 12 months of age.

7. Changes to the Product Information

As a result of this variation, section 5.1 of the SmPC is being updated to include information regarding the immune response induced by 2 doses of Nimenrix administered at 3 and 12 months of age.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

8. Request for supplementary information

Not applicable.