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Human Medicines Division

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No

Nimenrix

meningococcal group a, c, w135 and y conjugate vaccine

Procedure no: EMEA/H/C/002226/P46/057

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**	**Need for discussion**
☐	Start of procedure	25 Dec 2023	25 Dec 2023	☐
☐	CHMP Rapporteur Assessment Report	29 Jan 2024	29 Jan 2024	☐
☐	CHMP members comments	12 Feb 2024	12 Feb 2024	☐
☐	Updated CHMP Rapporteur Assessment Report	15 Feb 2024	15 Feb 2024	☐
☒	CHMP adoption of conclusions:	22 Feb 2024	22 Feb 2024	☐

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1. Introduction

On 29-Nov-2023, the MAH submitted a completed paediatric study for Nimenrix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study C0921062 "A Phase 3b Open-Label Study of 2 Doses of Nimenrix in Infants" is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

Nimenrix is a vaccine containing polysaccharides for *Neisseria meningitidis* groups A, C, W-135 and Y, each conjugated to a tetanus toxoid carrier. Nimenrix is indicated for active immunisation of individuals from the age of 6 weeks against invasive meningococcal disease caused by *Neisseria meningitidis* groups A, C, W-135 and Y. One dose (0.5mL) contains 5 micrograms of each polysaccharide conjugated to 44 micrograms of tetanus toxoid. There is no specific paediatric formulation, rather that the number of doses is adjusted according to age.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- C0921062 "A Phase 3b Open-Label Study of 2 Doses of Nimenrix in Infants".

2.3.2. Clinical study C0921062

Description

This Phase 3b, multicentre, open-label study, with a single-arm design, was conducted at investigator sites in Europe. The purpose of this study was to evaluate the safety and immunogenicity of a single dose of Nimenrix in infants at 3 months of age, followed by a second dose at 12 months of age. 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.

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 second 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. E-diaries were used to collect local reaction and systemic event data for 7 days after each vaccination. Adverse events (AEs) were

collected through 1 month after each vaccination. In addition, serious adverse events (SAEs) and newly diagnosed chronic medical conditions (NDCMCs) were collected throughout the study from Visit 1 through Visit 4 (1 month after Vaccination 2).

Methods

Study participants

The study enrolled healthy male or female infants, three months of age (≥76 to ≤ 104 days) at the time of consent (by parent/legal guardian) who 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. Infants were excluded if they had known or suspected immunodeficiency or immunosuppressive condition.

Non-study vaccines (other than meningococcal vaccine groups A, C, W or Y) that are part of recommended immunisation schedules were allowed any time during the study but were not to be administered within 14 days (for non-live vaccines) and 28 days (for live vaccines) of study administration. Tetanus-containing vaccines were allowed any time during the study (and can be given at the same time as study vaccine) but were not to be administered within 30 days before study vaccine.

Non-study vaccines used in the event of a disease outbreak or pandemic were allowed. However, efforts should be made not to administer non-study vaccines within 14 days (non-live) or 28 (live vaccines) days prior to study vaccine administration.

Treatments

Nimenrix (MenACWY-TT), 0.5 mL dose, supplied as a lyophilized powder in a single-dose vial to be reconstituted for injection and sodium chloride injection supplied in a PFS, to be given intramuscularly.

Objectives and endpoints

The purpose of the study was to evaluate the safety and immunogenicity of a single dose of Nimenrix in infants at 3 months of age, followed by a second dose at 12 months of age.

Study objectives and endpoints are presented in Table 1.

Table 1: Objectives and Endpoints

Objectives	Estimands	Endpoints
Primary (Safety):	**Primary (Safety):**	**Primary (Safety):**
• To describe the safety of 2 doses of Nimenrix when administered in healthy infants at 3 and 12 months of age.	In participants receiving Dose 1 and 2: • The percentage of participants reporting local reactions, systemic events, and use of antipyretic medication within 7 days after Dose 2 (Visit 3, 12 months of age) of Nimenrix. • The percentage of participants reporting at least 1 AE, at least 1 SAE, and at least 1 NDCMC during the following time period: • Within 30 days after Dose 2 (Visit 3, 12 months of age) of Nimenrix. • The percentage of participants reporting at least 1 immediate AE after Dose 2 (Visit 3, 12 months of age) of Nimenrix.	• Local reactions (redness, swelling, and pain at the injection site). • Systemic events (fever, decreased appetite, drowsiness, and irritability). • AEs. • SAEs. • NDCMCs.
Primary (Immunogenicity):	**Primary (Immunogenicity):**	**Primary (Immunogenicity):**
• 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.	In participants receiving both doses of Nimenrix and who are in compliance with the key protocol criteria (evaluable participants): • Percentage of participants with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY titers ≥1:8 for each serogroup at baseline (Visit 1, 3 months of age), at 1 month after Dose 1 (Visit 2, 4 months of age), at Dose 2 (Visit 3, 12 months of age), and at 1 month after Dose 2 (Visit 4, 13 months of age) of Nimenrix. • rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY GMTs for each serogroup at baseline (Visit 1, 3 months of age), at 1 month after Dose 1 (Visit 2, 4 months of age), at Dose 2 (Visit 3, 12 months of age), and at 1 month after Dose 2 (Visit 4, 13 months of age) of Nimenrix.	• rSBA titers for each of the MenA, MenC, MenW-135, and MenY serogroups.
Secondary:	**Secondary:**	**Secondary:**
• To describe the safety of 1 dose of Nimenrix when administered in healthy infants at 3 months of age.	In participants receiving at least 1 dose of study intervention: • The percentage of participants reporting local reactions, systemic events, and use of antipyretic medication within 7 days after Dose 1 (Visit 1, 3 months of age) of Nimenrix. • The percentage of participants reporting at least 1 AE, at least 1 SAE, and at least 1 NDCMC during the following time period:	• Local reactions (redness, swelling, and pain at the injection site). • Systemic events (fever, decreased appetite, drowsiness, and irritability). • AEs. • SAEs.

Objectives	Estimands	Endpoints
	• Within 30 days after Dose 1 (Visit 1, 3 months of age) of Nimenrix. • The percentage of participants reporting at least 1 SAE and at least 1 NDCMC during the following time periods: • During the follow-up phase: From 1 month after Dose 1 (Visit 2, 4 months of age) through 9 months after Dose 1 (Visit 3, 12 months of age) of Nimenrix. • 9 Months after the vaccination: From Dose 1 (Visit 1, 3 months of age) through 9 months after Dose 1 (Visit 3, 12 months of age) of Nimenrix. • The percentage of participants reporting at least 1 immediate AE after Dose 1 (Visit 1, 3 months of age) of Nimenrix.	• NDCMCs.
• To describe the immune response for *N meningitidis* serogroups A, C, W-135, and Y induced by 1 dose of Nimenrix administered at 3 months of age.	In participants who have received the first dose of Nimenrix and who are in compliance with the key protocol criteria (evaluable participants): • Percentage of participants with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY titers ≥1:8 for each serogroup at baseline (Visit 1, 3 months of age) and at 1 month after Dose 1 (Visit 2, 4 months of age) of Nimenrix. • rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY GMTs for each serogroup at baseline (Visit 1, 3 months of age) and at 1 month after Dose 1 (Visit 2, 4 months of age) of Nimenrix. • Percentage of participants with hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY titers ≥1:4, ≥1:8 for each serogroup at baseline (Visit 1, 3 months of age) and at 1 month after Dose 1 (Visit 2, 4 months of age) of Nimenrix. • hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY GMTs for each serogroup at baseline (Visit 1, 3 months of age) and at 1 month after Dose 1 (Visit 2, 4 months of age) of Nimenrix. • Percentage of participants with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY titers ≥1:128 for each serogroup at baseline (Visit 1, 3 months of age) and at 1 month after Dose 1 (Visit 2, 4 months of age) of Nimenrix.	• rSBA titers for each of the MenA, MenC, MenW-135, and MenY serogroups. • hSBA titers for each of the MenA, MenC, MenW-135, and MenY serogroups.

Objectives	Estimands	Endpoints
• To further 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.	• In participants who have received the first and second dose of Nimenrix and who are in compliance with the key protocol criteria (evaluable participants): • Percentage of participants with hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY titers ≥1:4, ≥1:8 for each serogroup at baseline (Visit 1, 3 months of age), at 1 month after Dose 1 (Visit 2, 4 months of age), at Dose 2 (Visit 3, 12 months of age), and at 1 month after Dose 2 (Visit 4, 13 months of age) of Nimenrix. • hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY GMTs for each serogroup at baseline (Visit 1, 3 months of age), at 1 month after Dose 1 (Visit 2, 4 months of age), at Dose 2 (Visit 3, 12 months of age), and at 1 month after Dose 2 (Visit 4, 13 months of age) of Nimenrix. • Percentage of participants with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY titers ≥1:128 for each serogroup at baseline (Visit 1, 3 months of age), at 1 month after Dose 1 (Visit 2, 4 months of age), at Dose 2 (Visit 3, 12 months of age), and at 1 month after Dose 2 (Visit 4, 13 months of age) of Nimenrix.	• hSBA titers for each of the MenA, MenC, MenW-135, and MenY serogroups. • rSBA titers for each of the MenA, MenC, MenW-135, and MenY serogroups.
Exploratory (Immunogenicity):	**Exploratory (Immunogenicity):**	**Exploratory (Immunogenicity):**
• N/A	• N/A	• N/A

Sample size

The study sample size was not based on any hypothesis testing criteria. All statistical analyses of immunogenicity and safety were descriptive. The study aimed to enrol approximately 150 participants, where based on a 15% exclusion rate that there would be approximately 130 evaluable participants.

Study conduct

The study began in April 2021 and completed recruitment in September 2021. The last participant completed Visit 4 (1 month after Vaccination 2) in September 2022. The COVID-19 pandemic was ongoing for the duration of the study.

There were no changes to the conduct of the study, and no amendments as a result of the COVID-19 pandemic.

Major protocol deviations were visits conducted out of window (n=20), receipt of non-study vaccine within a prohibited timeframe (n=15), procedures or tests not performed (n=11), administration at a site other than the left thigh (n=2), receipt on non-study meningococcal vaccine (MenC) during study (n=1), incorrect age at time of vaccination (n=1), vaccination despite need for temporary delay according to inclusion criteria (n=1), lack of e-Diary set up/completed during the 7-day post-dose reporting period.

Randomisation and blinding (masking)

The study was open label with one vaccine group.

Statistical Methods

The analysis populations are described in Table 2.

Table 2: Analysis populations for study C0921062

Population	Description
Enrolled	All participants, or participant's parent(s)/legal guardian(s), who sign the ICD.
Evaluable	Defined according to post–Vaccination 1 evaluable and post–Vaccination 2 evaluable criteria.
mITT	Defined according to post–Vaccination 1 and post–Vaccination 2 criteria.
Safety	All enrolled participants who receive at least 1 dose of the investigational product and have safety data reported after vaccination.
Defined Population for Analysis	**Description**
Post–Vaccination 1 evaluable immunogenicity population	1. Were enrolled and eligible through Visit 2. 2. Received the investigational product at Visit 1. 3. Had blood drawn for assay testing within the required time frames at Month 0 (Visit 1; before Vaccination 1) and Month 1 (Visit 2; 1 month after Vaccination 1: window 28-42 days). 4. Had at least 1 valid and determinate MenA, MenC, MenW- 135, and MenY assay result at Visit 2 (1 month after Vaccination 1). 5. Had received no prohibited vaccines or medications through Visit 2. 6. Had no major protocol deviations through Visit 2.
Post–Vaccination 2 evaluable immunogenicity population	1. Were enrolled and eligible through 1 month after Vaccination 2 of Nimenrix. 2. Received the investigational products at Visit 1 and Visit 3. 3. Had blood drawn for assay testing within the required time frames at Month 0 (Visit 1; before Vaccination 1) and at 1 month after Vaccination 2 (Visit 4; 1 month after Vaccination 2: window 28-42 days). 4. Had at least 1 valid and determinate MenA, MenC, MenW-135, and MenY assay result at Visit 4 (1 month after Vaccination 2). 5. Had received no prohibited vaccines or medications through Visit 4. 6. Had no major protocol deviations through Visit 4.
Post–Vaccination 1 mITT	All participants who received at least 1 dose of Nimenrix and had at least 1 valid and determinate MenA, MenC, MenW-135, and MenY assay result available at Visit 2.
Post–Vaccination 2 mITT	All participants who received 2 doses of Nimenrix and had at least 1 valid and determinate MenA, MenC, MenW-135, and MenY assay result available at Visit 4.
Vaccination 1 safety population	This population will include participants who received the first dose of investigational product at Visit 1 and for whom safety information is available from Visit 1 to prior to Visit 3.
Vaccination 2 safety population	This population will include participants who received the first and second dose of investigational product at Visit 1 and Visit 3 and for whom safety information is available from Visit 3.

If there was less than a 10% difference in the total number of participants included between the mITT and evaluable populations, only the evaluable population was used in the analysis of immunogenicity results.

Results

Participant flow

The majority (96.0%) of the 149 participants completed the study. 98.7% and 96.0% of participants were vaccinated with Vaccinations 1 and 2, respectively.

In total, 2 (1.3%) participants withdrew before vaccination and 4 participants withdrew after Vaccination 1. The reasons for withdrawal after vaccination were withdrawal by parent/guardian (3

participants) and lost to follow-up (1 participant). No participants withdrew within 1 month after Vaccination 2. There were no withdrawals due to AEs.

Recruitment

A total of 149 participants were enrolled at 14 centres in 3 countries (97 participants in Finland, 27 participants in Poland, and 25 participants in Spain).

Baseline data

Demographic characteristics are presented in Table 3. The mean age at Vaccination 1 (Visit 1) was 94.4 days and 52.4% of participants were female. The majority (97.2%) of participants were white and 65.5% of participants were enrolled in Finland.

Table 3: Demographic Characteristics – Safety Population

	Vaccine Group Nimenrix (N[a]=145) n[b] (%)
Sex	
Female	76 (52.4)
Male	69 (47.6)
Race	
Black or African American	0
Asian	1 (0.7)
White	141 (97.2)
Multiracial[c]	2 (1.4)
Not reported	1 (0.7)
Ethnicity	
Hispanic or Latino	26 (17.9)
Non-Hispanic or non-Latino	119 (82.1)
Not reported	0
Country	
Finland	95 (65.5)
Poland	26 (17.9)
Spain	24 (16.6)
Age at first vaccination (days)	
n	145
Mean (SD)[d]	94.4 (6.09)
Median (Q1,Q3)[e]	94.0 (91.0, 99.0)
Min, max	(78, 105)

a. N = number of participants in the total sample. This value is used as the denominator for the percentage calculations.
b. n = Number of participants in the specified category.
c. Multiracial: where more than one category is selected for race.
d. SD = standard deviation.
e. Q1/Q3 = 1st/3rd quartile (25th and 75th percentile).

Numbers analysed

The majority of participants received Vaccination 1 (98.7%) and Vaccination 2 (96.0%). The majority (89.9%) of participants received Vaccination 2 within the protocol-specified time frame after Vaccination 1.

The majority of participants had a blood sample drawn within the protocol-specified time frame for each study visit: at or before Vaccination 1 (Day 1) (97.3%), 1 month (Days 28-42) after Vaccination 1 (89.3%), 9 months (Days 270-300) after Vaccination 1 (87.2%), and 1 month (Days 28-42) after Vaccination 2 (89.9%).

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. This was primarily as a result of indeterminate testing results (34.2% and 33.6% of all enrolled participants for MenW-135 before and at 1 month after Vaccination 1, respectively; 31.5% and 28.9% of all enrolled participants for MenY before and at 1 month after Vaccination 1, respectively).

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 SBAs at these timepoints were limited. Furthermore, rSBA testing was prioritized over hSBA testing because rSBA testing supported primary immunogenicity objectives. In addition, testing for MenA hSBA and MenC hSBA was prioritized over testing for MenW-135 hSBA and MenY hSBA.

The evaluable immunogenicity population was the primary immunogenicity population. Analyses for immunogenicity data were also performed on the mITT population. The populations are presented in Table 4.

Table 4: Evaluable Immunogenicity and mITT Population

	Vaccine Group Nimenrix n[a] (%)
Enrolled[b]	149
Post-Dose 1 mITT population	138 (92.6)
Excluded from PD1 mITT population	11 (7.4)
Post-Dose 1 evaluable immunogenicity population	116 (77.9)
Excluded from post-Dose 1 evaluable immunogenicity population	33 (22.1)
Reason for exclusion	
Were not enrolled or eligible through Visit 2	3 (2.0)
Did not receive investigational product at Visit 1	2 (1.3)
Did not have blood drawn or was outside the required time frame at Visit 1 (Month 0, before Dose 1) and Visit 2 (1 month after Dose 1)	17 (11.4)
Had no valid and determinate assay result at Visit 2	11 (7.4)
Had received prohibited vaccines or medications through Visit 2	14 (9.4)
Had important protocol deviations through Visit 2	0
Post-Dose 2 mITT population	140 (94.0)
Excluded from PD2 mITT population	9 (6.0)
Post-Dose 2 evaluable immunogenicity population	128 (85.9)
Excluded from post-Dose 2 evaluable immunogenicity population	21 (14.1)
Reason for exclusion	
Were not enrolled or eligible through Visit 4	3 (2.0)
Did not receive investigational product at Visit 1 and Visit 3	6 (4.0)
Did not have blood drawn or was outside the required time frames at Visit 1 (Month 0, before Dose 1) and Visit 4 (1 month after Dose 2)	16 (10.7)
Had no valid and determinate assay result at Visit 4	9 (6.0)
Had received prohibited vaccines or medications through Visit 4	4 (2.7)
Had important protocol deviations through Visit 4	0

a. n = Number of participants with the specified characteristic.
b. The value in this row is used as the denominator for percentage calculations.

Efficacy results

Primary Immunogenicity Endpoint

Percentage of participants with rSBA titres ≥ 1:8

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 5).

Table 5: Number (%) of Participants With rSBA Titers ≥1:8, ≥1:128 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)
		≥1:128	128	0	0.0	(0.0, 2.8)
	1 Month after Vaccination 1	≥1:8	124	102	82.3	(74.4, 88.5)
		≥1:128	124	50	40.3	(31.6, 49.5)
	Before Vaccination 2	≥1:8	125	42	33.6	(25.4, 42.6)
		≥1:128	125	19	15.2	(9.4, 22.7)
	1 Month after Vaccination 2	≥1:8	128	128	100.0	(97.2, 100.0)
		≥1:128	128	128	100.0	(97.2, 100.0)
MenC	Before Vaccination 1	≥1:8	128	6	4.7	(1.7, 9.9)
		≥1:128	128	1	0.8	(0.0, 4.3)
	1 Month after Vaccination 1	≥1:8	124	113	91.1	(84.7, 95.5)
		≥1:128	124	84	67.7	(58.8, 75.9)
	Before Vaccination 2	≥1:8	125	81	64.8	(55.8, 73.1)
		≥1:128	125	26	20.8	(14.1, 29.0)
	1 Month after Vaccination 2	≥1:8	128	128	100.0	(97.2, 100.0)
		≥1:128	128	126	98.4	(94.5, 99.8)
MenW-135	Before Vaccination 1	≥1:8	128	1	0.8	(0.0, 4.3)
		≥1:128	128	1	0.8	(0.0, 4.3)
	1 Month after Vaccination 1	≥1:8	124	111	89.5	(82.7, 94.3)
		≥1:128	124	99	79.8	(71.7, 86.5)
	Before Vaccination 2	≥1:8	125	84	67.2	(58.2, 75.3)
		≥1:128	125	29	23.2	(16.1, 31.6)
	1 Month after Vaccination 2	≥1:8	128	128	100.0	(97.2, 100.0)
		≥1:128	128	128	100.0	(97.2, 100.0)
MenY	Before Vaccination 1	≥1:8	128	10	7.8	(3.8, 13.9)
		≥1:128	128	5	3.9	(1.3, 8.9)
	1 Month after Vaccination 1	≥1:8	124	112	90.3	(83.7, 94.9)
		≥1:128	124	103	83.1	(75.3, 89.2)
	Before Vaccination 2	≥1:8	125	83	66.4	(57.4, 74.6)
		≥1:128	125	34	27.2	(19.6, 35.9)
	1 Month after Vaccination 2	≥1:8	128	128	100.0	(97.2, 100.0)
		≥1:128	128	127	99.2	(95.7, 100.0)

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. c. Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.

rSBA GMTs

At 1 month after Vaccination 1, rSBA GMTs increased (54.7 to 202.4) from baseline (4.0 to 5.0) across the 4 serogroups. 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 (1299.5 to 2714.1), as shown in Table 6.

Table 6: 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).

Secondary Endpoints

Percentage of Participants With rSBA ≥ 1:128

At baseline percentage of participants achieving rSBA titers ≥ 1:128 range from 0.0% to 3.9%. At 1 month after Vaccination 1, the proportion of participants achieving rSBA titers ≥1:128 ranged from 40.3% to 90.3% across the 4 serogroups. Prior to Vaccination 2, the proportion of participants with rSBA titers ≥1:128 ranged from 15.2% to 27.2% across the 4 serogroups. At 1 month after Vaccination 2 proportions ranged from 98.4% to 100.0% (Table 5).

Percentage of participants with hSBA titres ≥ 1:4 and ≥ 1:8

The percentage of participants with hSBA titres ≥1:4 at baseline ranged from 8.0% to 21.9%. At 1 month after Vaccination 1, the proportion of participants achieving hSBA titers ≥1:4 ranged from 38.8% to 95.5% across the 4 serogroups. Prior to Vaccination 2, the proportion of participants with hSBA titers ≥1:4 ranged from 49.1% to 94.0% across the 4 serogroups. For MenC, MenW-135 and MenY the proportion range from 70.8% to 94.0%, while for MenA the proportion was 49.1. At 1 month after Vaccination 2, all participants (100%) achieved hSBA titers ≥1:4 across all 4 serogroups.

Percentage of participants with hSBA titres ≥1:4 and ≥1:8 at the different timepoints is presented in Table 7.

Table 7: Number (%) of Participants With hSBA Titers ≥1:4, ≥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	≥1:4	100	8	8.0	(3.5, 15.2)
		≥1:8	100	7	7.0	(2.9, 13.9)
	1 Month after Vaccination 1	≥1:4	111	106	95.5	(89.8, 98.5)
		≥1:8	111	106	95.5	(89.8, 98.5)
	Before Vaccination 2	≥1:4	108	53	49.1	(39.3, 58.9)
		≥1:8	108	50	46.3	(36.7, 56.2)
	1 Month after Vaccination 2	≥1:4	123	123	100.0	(97.0, 100.0)
		≥1:8	123	123	100.0	(97.0, 100.0)
MenC	Before Vaccination 1	≥1:4	111	13	11.7	(6.4, 19.2)
		≥1:8	111	13	11.7	(6.4, 19.2)
	1 Month after Vaccination 1	≥1:4	116	108	93.1	(86.9, 97.0)
		≥1:8	116	108	93.1	(86.9, 97.0)
	Before Vaccination 2	≥1:4	121	103	85.1	(77.5, 90.9)
		≥1:8	121	103	85.1	(77.5, 90.9)
	1 Month after Vaccination 2	≥1:4	123	123	100.0	(97.0, 100.0)
		≥1:8	123	123	100.0	(97.0, 100.0)
MenW-135	Before Vaccination 1	≥1:4	65	8	12.3	(5.5, 22.8)
		≥1:8	65	8	12.3	(5.5, 22.8)
	1 Month after Vaccination 1	≥1:4	67	26	38.8	(27.1, 51.5)
		≥1:8	67	26	38.8	(27.1, 51.5)
	Before Vaccination 2	≥1:4	100	94	94.0	(87.4, 97.8)
		≥1:8	100	94	94.0	(87.4, 97.8)
	1 Month after Vaccination 2	≥1:4	119	119	100.0	(96.9, 100.0)
		≥1:8	119	119	100.0	(96.9, 100.0)
MenY	Before Vaccination 1	≥1:4	73	16	21.9	(13.1, 33.1)
		≥1:8	73	16	21.9	(13.1, 33.1)
	1 Month after Vaccination 1	≥1:4	72	36	50.0	(38.0, 62.0)
		≥1:8	72	36	50.0	(38.0, 62.0)
	Before Vaccination 2	≥1:4	106	75	70.8	(61.1, 79.2)
		≥1:8	106	75	70.8	(61.1, 79.2)
	1 Month after Vaccination 2	≥1:4	123	123	100.0	(97.0, 100.0)
		≥1:8	123	123	100.0	(97.0, 100.0)

Abbreviations: hSBA = serum bactericidal assay using human 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 hSBA 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 hSBA titer for the specified serogroup at the given time point. c. Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.

hSBA GMTs

At 1 month after Vaccination 1, hSBA GMTs increased (8.8 to 149.8) from baseline (2.4 to 5.7) across the 4 serogroups. Prior to Vaccination 2, hSBA GMTs were higher than baseline ranging from 9.5 to 121.6 across the 4 serogroups. At 1 month after Vaccination 2, hSBA GMTs further increased (1208.4 to 7299.6), see Table 8.

Table 8: hSBA 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	100	2.4	(2.1, 2.7)
	1 Month after Vaccination 1	111	86.9	(68.8, 109.8)
	Before Vaccination 2	108	9.5	(6.8, 13.2)
	1 Month after Vaccination 2	123	1208.4	(976.9, 1494.8)
MenC	Before Vaccination 1	111	2.9	(2.3, 3.6)
	1 Month after Vaccination 1	116	149.8	(111.3, 201.6)
	Before Vaccination 2	121	74.8	(52.3, 107.0)
	1 Month after Vaccination 2	123	7299.6	(5362.8, 9936.0)
MenW-135	Before Vaccination 1	65	2.8	(2.2, 3.5)
	1 Month after Vaccination 1	67	8.8	(5.5, 14.2)
	Before Vaccination 2	100	121.6	(90.0, 164.2)
	1 Month after Vaccination 2	119	6955.8	(5922.4, 8169.4)
MenY	Before Vaccination 1	73	5.7	(3.5, 9.5)
	1 Month after Vaccination 1	72	19.9	(10.8, 36.6)
	Before Vaccination 2	106	45.7	(28.8, 72.5)
	1 Month after Vaccination 2	123	5062.1	(4202.9, 6097.0)

Abbreviations: GMT = geometric mean titer; hSBA = serum bactericidal assay using human 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 = 1:4 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 hSBA titers for the specified serogroup at the given time point.
b. GMTs are calculated using all participants with valid and determinate hSBA titers at the given time point.
c. CIs are obtained by exponentiating the limits of CIs for the mean logarithm of the hSBA titers (based on the Student t distribution).

A substantial proportion of participants did not contribute to the immunogenicity evaluation for hSBA MenW-135 and hSBA MenY before Vaccination 1 and at 1 month after Vaccination 1 primarily due to indeterminate results and quantity not sufficient. Consequently, the MenW-135 and MenY hSBA results for these blood sampling points were based on a limited number of participants.

Safety results

The safety population included 145 participants that received vaccination 1 and 143 participants that received dose two.

The majority of the participants where white (97.6%), 1.4% multiracial, 0.7% Asian, and 0.7% not reported. 17.9% were Hispanic or Latino and the majority non-Hispanic or non-Latino (82.1%). The participants were from Finland (65.5%), Poland (17.9%) and Spain (16.6%).

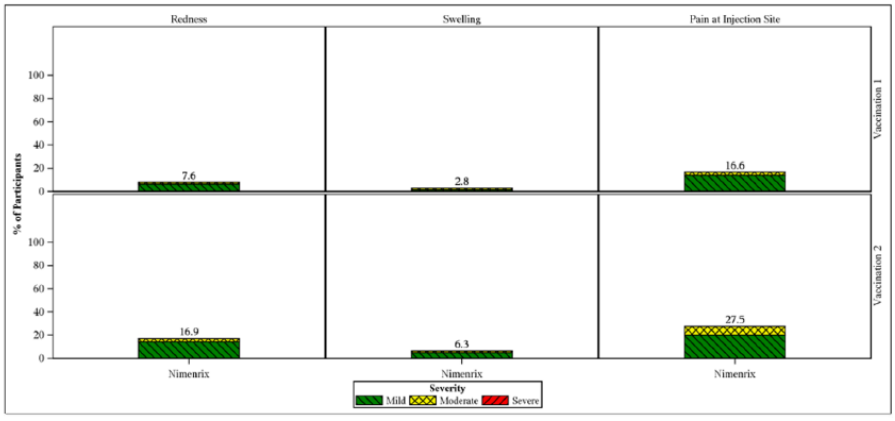
Non-study vaccines that were part of recommended immunization schedules (including meningococcal B vaccines) could be administered any time during the study but should not be administered within 14 days (for non-live vaccines) and 28 days (for live vaccines) as per protocol. In total, 110 (75.9%) participants received a non-study vaccine on the same day as Vaccination 1 and 88 (61.5%) participants received a non-study vaccine on the same day as Vaccination 2 (Table 9).

Table 9: Non-study Vaccines Received On the Same Day as Study Vaccine

Vax No.	Nonstudy Vaccine and Allergen Immunotherapy[a]	Vaccine Group Nimenrix n[b] (%)
1 (N[c]=145)	Any vaccine type	110 (75.9)
	DIPHTHERIA VACCINE TOXOID;HEPATITIS B VACCINE RHBSAG;HIB VACCINE CONJ (TET TOX);PERTUSSIS VACCINE ACELLULAR 2-COMPONENT;POLIO VACCINE INACT 3V (VERO);TETANUS VACCINE TOXOID	1 (0.7)
	DIPHTHERIA VACCINE TOXOID;HIB VACCINE CONJ (TET TOX);PERTUSSIS VACCINE ACELLULAR 2-COMPONENT;POLIO VACCINE INACT 3V (VERO);TETANUS VACCINE TOXOID	86 (59.3)
	DIPHTHERIA VACCINE;HIB VACCINE;PERTUSSIS VACCINE ACELLULAR;POLIO VACCINE INACT;TETANUS VACCINE	5 (3.4)
	MENINGOCOCCAL VACCINE B RFHBP/NADA/NHBA OMV	14 (9.7)
	PNEUMOCOCCAL VACCINE CONJ 10V	91 (62.8)
	PNEUMOCOCCAL VACCINE CONJ 13V (CRM197)	1 (0.7)
	ROTAVIRUS VACCINE LIVE ORAL 1V	1 (0.7)
	ROTAVIRUS VACCINE LIVE REASSORT ORAL 5V	96 (66.2)
2 (N[c]=143)	Any vaccine type	88 (61.5)
	DIPHTHERIA VACCINE TOXOID;HIB VACCINE CONJ (TET TOX);PERTUSSIS VACCINE ACELLULAR 2-COMPONENT;POLIO VACCINE INACT 3V (VERO);TETANUS VACCINE TOXOID	69 (48.3)
	DIPHTHERIA VACCINE;HIB VACCINE;PERTUSSIS VACCINE ACELLULAR;POLIO VACCINE INACT;TETANUS VACCINE	4 (2.8)
	MEASLES VACCINE LIVE (ENDERS-EDMONSTON);MUMPS VACCINE LIVE (JERYL LYNN);RUBELLA VACCINE LIVE (WISTAR RA 27/3)	66 (46.2)
	MEASLES VACCINE;MUMPS VACCINE;RUBELLA VACCINE	6 (4.2)
	MENINGOCOCCAL VACCINE B RFHBP/NADA/NHBA OMV	11 (7.7)
	PNEUMOCOCCAL VACCINE CONJ 10V	74 (51.7)
	VARICELLA ZOSTER VACCINE LIVE (OKA/MERCK)	1 (0.7)
Any vaccine (N[c]=145)	Any vaccine type	116 (80.0)

Local reactogenicity and systemic events (solicited AEs) were assessed from day 1 to day 7 following vaccination 1 and 2 and reported in the e-diary.

Figure 1: Local Reactions, by Maximum Severity, Within 7 Days After Vaccination – Safety Population



Overall, local reactions were predominantly mild with pain at the injection site being the most commonly reported local reaction (Figure 1). No severe or Grade 4 local reactions were reported and no local reaction led to study withdrawal. The median onset of local reactions was 1 day and the duration of local reactions was 1.0 to 2.0 days, with a maximum duration of redness of up to 6 days after Vaccination 2. No local reactions had a duration greater than 14 days during the study.

Systemic events

Figure 2: Systemic Events for Fever, Decreased Appetite, Increased Sleep and Irritability, by Maximum Severity, Within 7 Days After Vaccination - Safety Population

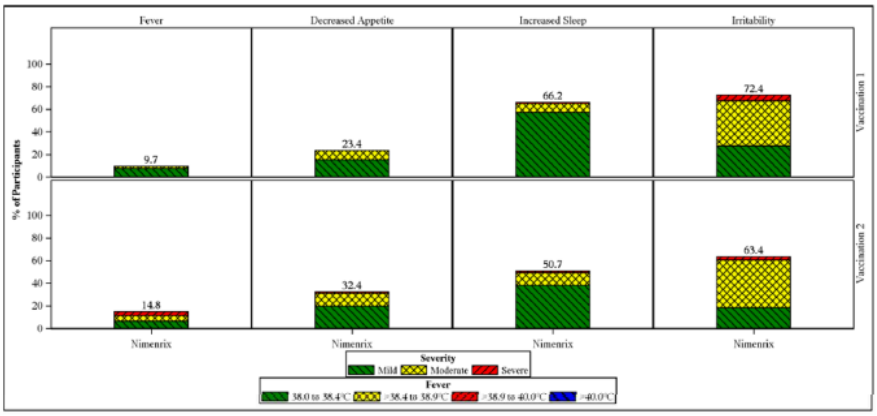


Table 10: Participants Reporting Systemic Events by Severity, Within 7 Days After Each Vaccination - Safety Population

		Vaccine Group Nimenrix		
Vax No.	Systemic Event Severity	N[a]	n[b](%)	(95% CI[c])
1	Fever(≥38.0°C)			
	≥38.0°C	145	14 (9.7)	(5.4, 15.7)
	≥38.0°C to 38.4°C	145	11 (7.6)	(3.8, 13.2)
	>38.4°C to 38.9°C	145	3 (2.1)	(0.4, 5.9)
	>38.9°C to 40.0°C	145	0	(0.0, 2.5)
	>40.0°C	145	0	(0.0, 2.5)
	Decreased Appetite[d]			
	Any	145	34 (23.4)	(16.8, 31.2)
	Mild	145	22 (15.2)	(9.8, 22.1)
	Moderate	145	12 (8.3)	(4.3, 14.0)
	Severe	145	0	(0.0, 2.5)
	Increased Sleep[e]			
	Any	145	96 (66.2)	(57.9, 73.8)
	Mild	145	83 (57.2)	(48.8, 65.4)
	Moderate	145	11 (7.6)	(3.8, 13.2)
	Severe	145	2 (1.4)	(0.2, 4.9)
	Irritability[f]			
	Any	145	105 (72.4)	(64.4, 79.5)
	Mild	145	40 (27.6)	(20.5, 35.6)
	Moderate	145	58 (40.0)	(32.0, 48.5)
	Severe	145	7 (4.8)	(2.0, 9.7)
	Any systemic event[g]	145	126 (86.9)	(80.3, 91.9)
	Use of antipyretic or pain medication[h]	145	57 (39.3)	(31.3, 47.8)
2	Fever(≥38.0°C)			
	≥38.0°C	142	21 (14.8)	(9.4, 21.7)
	≥38.0°C to 38.4°C	142	9 (6.3)	(2.9, 11.7)
	>38.4°C to 38.9°C	142	7 (4.9)	(2.0, 9.9)
	>38.9°C to 40.0°C	142	5 (3.5)	(1.2, 8.0)
	>40.0°C	142	0	(0.0, 2.6)
	Decreased Appetite[d]			
	Any	142	46 (32.4)	(24.8, 40.8)
	Mild	142	28 (19.7)	(13.5, 27.2)

Vax No.	Systemic Event Severity	Vaccine Group Nimenrix N[a]	n[b](%)	(95% CI[c])
	Moderate	142	16 (11.3)	(6.6, 17.7)
	Severe	142	2 (1.4)	(0.2, 5.0)
	Increased Sleep[e]			
	Any	142	72 (50.7)	(42.2, 59.2)
	Mild	142	54 (38.0)	(30.0, 46.5)
	Moderate	142	16 (11.3)	(6.6, 17.7)
	Severe	142	2 (1.4)	(0.2, 5.0)
	Irritability[f]			
	Any	142	90 (63.4)	(54.9, 71.3)
	Mild	142	26 (18.3)	(12.3, 25.7)
	Moderate	142	60 (42.3)	(34.0, 50.8)
	Severe	142	4 (2.8)	(0.8, 7.1)
	Any systemic event[g]	142	107 (75.4)	(67.4, 82.2)
	Use of antipyretic or pain medication[h]	142	79 (55.6)	(47.1, 64.0)
Any vaccination	Fever(≥38.0°C)			
	≥38.0°C	145	31 (21.4)	(15.0, 29.0)
	≥38.0°C to 38.4°C	145	16 (11.0)	(6.4, 17.3)
	>38.4°C to 38.9°C	145	10 (6.9)	(3.4, 12.3)
	>38.9°C to 40.0°C	145	5 (3.4)	(1.1, 7.9)
	>40.0°C	145	0	(0.0, 2.5)
	Decreased Appetite[d]			
	Any	145	65 (44.8)	(36.6, 53.3)
	Mild	145	39 (26.9)	(19.9, 34.9)
	Moderate	145	24 (16.6)	(10.9, 23.6)
	Severe	145	2 (1.4)	(0.2, 4.9)
	Increased Sleep[e]			
	Any	145	115 (79.3)	(71.8, 85.6)
	Mild	145	84 (57.9)	(49.5, 66.1)
	Moderate	145	27 (18.6)	(12.6, 25.9)
	Severe	145	4 (2.8)	(0.8, 6.9)
	Irritability[f]			
	Any	145	119 (82.1)	(74.8, 87.9)
	Mild	145	31 (21.4)	(15.0, 29.0)
	Moderate	145	78 (53.8)	(45.3, 62.1)
	Severe	145	10 (6.9)	(3.4, 12.3)
	Any systemic event[g]	145	136 (93.8)	(88.5, 97.1)
	Use of antipyretic or pain medication[h]	145	96 (66.2)	(57.9, 73.8)

a. N = number of participants reporting at least 1 yes or no response for the specified reaction. These values are used as the denominators for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Exact 2-sided confidence interval (CI), based on the Clopper and Pearson method.
d. Mild = decreased interest in eating; moderate = decreased oral intake; severe = refusal to feed.
e. Mild = increased or prolonged sleeping bouts; moderate = slightly subdued, interfering with daily activity; severe = disabling, not interested in usual daily activity.
f. Mild = easily consolable; moderate = requiring increased attention; severe = inconsolable, crying, cannot be comforted.
g. Any systemic event = any fever≥38.0°C, any decreased appetite, any drowsiness, any irritability.
h. Severity is not collected for use of antipyretic or pain medication.
PFIZER CONFIDENTIAL SDTM Creation: 07OCT2022 (13:17) Source Data: adfacevd Table Generation: 14OCT2022 (14:21)
Output File: ./nda1_cdisc/C0921062/adce_s020_se_maxsev_saf

Overall, systemic events were predominantly mild or moderate, with irritability and increased sleep the most commonly reported systemic events (Figure 2). No participants reported fever >40.0°C and no Grade 4 systemic events were reported (Table 10). No systemic events led to study withdrawal. The median onset of systemic events was 1-2 days and median duration of systemic events was 1.0 to 3.0 days, with a maximum duration of fever and irritability of up to 14 days after Vaccination 2.

Antipyretic or pain medication use was reported by 57 (39.3%) participants after Vaccination 1 and by 79 (55.6%) participants after Vaccination 2.

Unsolicited AEs

Unsolicited AEs were collected within 30 days after vaccination. AEs were reported in 10 (6.9%) and 28 participants (19.6%) after the first and second vaccination, respectively (35 participants; 24.1% after any vaccination). The most commonly reported SOC after any vaccination was infections and

infestations. The most frequently reported preferred terms (PTs) after any vaccination were upper respiratory tract infection, nasopharyngitis, laryngitis, and pyrexia. No immediate AEs were reported within the 30-minute observation period immediately after Vaccination 1 or Vaccination 2.

No related AEs were reported within 30 days after Vaccination 1. One (0.7%) participant reported moderate pyrexia and moderate irritability after Vaccination 2 which were reported as related AEs as the caregiver missed reporting the events in the e-diary.

Serious AEs

After Vaccination 1, 8 (5.5%) participants reported 8 SAEs and 2 (1.4%) participants reported 2 SAEs after Vaccination 2. The most frequently reported SAEs by PT were respiratory syncytial virus bronchiolitis (3 [2.1%] participants [3 events]) and respiratory syncytial virus infection (2 [1.4%] participants [2 events]). None of the SAEs were considered related to Nimenrix.

The overall safety data demonstrated that Nimenrix was well tolerated with a low incidence of severe and related AEs. Related AEs were attributable to reactogenicity events. The proportion of participants who reported SAEs was low and none were related to the vaccine. There were no deaths, and no participants withdrew from the study due to AEs.

Overall, safety results from participants who received Nimenrix at 3 and 12 months of age demonstrated that Nimenrix was safe and well tolerated and did not suggest any safety issues. The safety profile of Nimenrix given at 3 and 12 months of age is consistent with the known safety profile of the vaccine in the infant population when 2 doses of Nimenrix are given before 6 months of age with a booster at 12 months, and a single dose of Nimenrix is given at 6 months in infants from 6 months of age with a booster dose at 12 months as described in the Nimenrix SmPC.

Treatment discontinuation

No participants discontinued or withdrew from the study because of AEs.

Adverse events of special interest (AESI) and NDCMC

There was one case of food protein induced enterocolitis syndrome 100 days after vaccination reported as not related by the investigator. No NDCMC were reported.

Deaths

None.

2.3.3. Discussion on clinical aspects

Immunogenicity:

The primary immunogenicity endpoint of study C0921062 is based on rSBA titres. The rSBA may give higher titres compared to those obtained with hSBA. For hSBA a titre $\geq$ 1:4 is widely accepted as a correlate of protection. hSBA titres are nevertheless included as a secondary endpoint, making an evaluation of both rSBA and hSBA titres possible. However, since it was difficult to obtain sufficient blood volumes in children in this age group (3 months) and the fact that rSBA levels were prioritised (primary endpoint), the data for MenW-135 and MenY is limited regarding hSBA titres and GMT.

Based on the available immunogenicity data, Nimenrix given at 3 and 12 months of age provided rSBA titers indicative of protection 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 immunogenicity results as measured by

rSBA GMTs indicate a substantial increase in GMTs from baseline following Vaccination 1 and an anamnestic response following Vaccination 2 across all 4 serogroups.

The study underlines the importance of a booster dose at 12 months, with 100 % of participants achieving an rSBA titre $\geq$ 1:8 and a hSBA titre $\geq$ 1:4 one month after dose 2 (12 months). 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.

The percentage of participants with rSBA titres $\geq$ 1:8 and $\geq$ 1:128 falls at the timepoint before vaccination 2. This is also seen in the rSBA GMTs, however, the GMTs still remain over baseline values. This drop is not as prominent when considering hSBA titres. For serogroups C, W-135 and Y the proportion of participants with a hSBA titre $\geq$ 1:4 remains relatively high until vaccination 2, although there is a more pronounced drop for MenA. This is also seen when looking at the hSBA GMTs. Nevertheless, there is a substantial increase in both rSBA and hSBA GMTs post dose 2, further highlighting the importance of a dose at 12 months.

The GMT (rSBA and hSBA) 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 >1:8 for both hSBA and rSBA was >89% for all groups. Following booster immunisation at 12 months, the GMT appear comparable and 100% achieved a titre >1:8 whereas in section 5.1 this was >98.4% for all groups. Since information the sample size for MenW-135 and MenY is lower following a single dose, the level of protection afforded with a single dose Nimenrix in this age group is uncertain.

Regarding hSBA titres for MenW-135 and MenY, both the proportion of participants achieving a titre $\geq$ 1:4 and 1:8 and GMTs are higher before vaccination 2 compared to one month after vaccination 1. The MAH explained that 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.

The MAH concludes that a single immunisation at 3 months of age followed by a booster at 12 months could be an alternative immunisation schedule for the vaccination of healthy infants. However, there is no information in the documentation as to whether the MAH considers an update to the SmPC necessary. As per 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*". Information on the response of a second dose at 12 months could be considered relevant, especially in instances where a child has, for some reason, not received the second dose two months after the first, as according to the posology. The data provided is currently considered insufficient to warrant a change to the current posology for the age group 6 weeks to <6 months, however, prescribers can be informed on the potential for protection, should only a single dose have been administered in this age group. The data emphasise the importance of the booster dose at 12 months of age.

Safety:

Study C0921062 was a phase 3, single arm, open label study with 80% of the participant receiving Nimenrix concomitantly with other non-study vaccines. The lack of a comparator group that received two doses at 3 and 12 months and the high rate of co-administration with other vaccines precludes a meaningful comparison with other studies previously conducted.

However, the provided safety data does not raise any new safety concerns and is consistent with the safety profile of Nimenrix as described in the Nimenrix SmPC. In conclusion, the safety data from this study is not considered to be sufficient to warrant an update of the SmPC with safety information regarding 3 and 12 months vaccination schedule in 4.8 from a safety point of view. The MAH states that the information that Nimenrix can be safely administered as 1 dose at 3 months and 1 dose at 12 months can be important for clinicians. However, no information is provided in the documentation if the MAH considers that an update of the SmPC is warranted despite the phrasing.

3. CHMP overall conclusion and recommendation

The data for study C0921062 should be included in section 5.1 of the SmPC as additional information for prescribers. However, the data is considered insufficient to warrant any changes to the current posology in the age group 6-weeks to less than 6 months of age. Safety data from this study is not considered sufficient for inclusion in 4.8 of the SmPC.

☒ Fulfilled:

In view of the available data regarding study C0921062, the MAH should either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. This should be provided without any delay and ***no later than 60 days after the receipt*** of these conclusions.