22 June 2023
EMA/CHMP/199192/2023
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Nimenrix

meningococcal group a, c, w135 and y conjugate vaccine

Procedure no: EMEA/H/C/002226/P46/056

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	27 Mar 2023	27 Mar 2023	☐
☐	CHMP Rapporteur Assessment Report	02 May 2023	02 May 2023	☐
☐	CHMP members comments	15 May 2023	15 May 2023	☐
☐	Updated CHMP Rapporteur Assessment Report	17 May 2023	17 May 2023	☐
☐	CHMP adoption of conclusions:	25 May 2023	25 May 2023	☐
☐	Submission	30 May 2023	30 May 2023	☐
☐	Re-start	31 May 2023	31 May 2023	☐
☐	CHMP Rapporteur Assessment Report	07 Jun 2023	07 Jun 2023	☐
☐	CHMP members comments	12 Jun 2023	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	15 Jun 2023	n/a	☐
☒	CHMP adoption of conclusions:	22 Jun 2023	22 Jun 2023	☐

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1. Introduction

On 15 March 2023, the MAH submitted a completed paediatric study for Nimenrix, in accordance with Article 46 of Regulation (EC) No0901/2006 as amended.

A short critical expert overview has also been provided.

Nimenrix has been used as a comparator in a clinical study investigating the meningococcal pentavalent vaccine (MenABCWY) in children aged 2 to 6 months of age. MenABCWY is a combination of the approved vaccines Nimenrix (MenACWY-TT) and Trumenba (MenB).

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the study entitled "A phase 2b trial to assess the safety, tolerability and immunogenicity of MenABCWY in healthy infants 2 and 6 months of age" with identification number C3511002 is part of a clinical development program for MenABCWY where Nimenrix and Bexsero have each been used as comparators.

2.2. Information on the pharmaceutical formulation used in the study

Nimenrix is approved for active immunisation in children from 6 weeks of age against invasive meningococcal disease caused by Neisseria meningitidis groups A, C, W-135 and Y. Trumenba is approved for active immunisation in individuals 10 years and older to prevent invasive meningococcal disease caused by Neisseria meningitidis serogroup B.

MenABCWY is an investigative product where Nimenrix and Trumenba are combined in the same vial. The clinical study of MenABCWY described in this report recruiting children aged two to six months involves the use of Trumenba outside the current indication.

Bexsero is indicated for the active immunisation of individuals from 2 months of age and older against invasive meningococcal disease caused by Neisseria meningitidis group B and was also used as a comparator.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

• Study C3511002 (EudraCT number: 2020-000948-60): A phase 2b trial to assess the safety, tolerability, and immunogenicity of MenABCWY in healthy infants 2 and 6 Months of Age.

2.3.2. Clinical study C3511002

Description

Study C3511002 was designed to describe the safety, tolerability, and immunogenicity of MenABCWY in healthy infants, beginning with infants 6 months of age and progressing to infants 2 months of age. The investigational meningococcal pentavalent vaccine (MenABCWY) is composed of licensed vaccines Trumenba (serogroup B; bivalent rLP2086) and Nimenrix (groups A, C, W-135, and Y; MenACWY-TT). The bivalent rLP2086 was supplied as a 0.7-mL prefilled syringe and MenACWY-TT was supplied as a

lyophilized vial. The final product consisted of reconstitution of MenACWY-TT in the bivalent rLP2086 in liquid form.

In this study, Nimenrix was used as comparator. Participants were randomized to receive one of the following:

- MenABCWY [single injection];
- Bivalent rLP2086 (60-µg or 120-µg dose level) and Nimenrix [co-administration], or;
- Bexsero (4CMenB) and Nimenrix [co-administration].

In addition, all participants received the licensed vaccines DTaP-HBV-IPV/Hib (Vaxelis) and the pneumococcal vaccine Prevenar 13 concomitantly with the administration of the study vaccines.

The safety, tolerability, and immunogenicity of MenABCWY were to be evaluated and compared with co-administration of the licensed vaccines Bexsero and Nimenrix in this same age group.

The study was designed with an open-label sentinel phase followed by expanded enrolment stages (see **Table *1***).

Pfizer made the decision to terminate the study early after review of all safety data, including 2 cases of cerebrospinal fluid (CSF) pleocytosis that occurred in this study in 2-month-old infants receiving either bivalent rLP2086 co-administered with Nimenrix or MenABCWY, and a third case from Study B1971008 (early terminated more than 10 years ago) in a 2-month-old infant who was hospitalised within 2 days of vaccination, with evaluations also having revealed CSF pleocytosis. The decision was in accordance with a recommendation by the EDMC after they reviewed all the available safety data. The cases of CSF pleocytosis were limited to participants less than 6 months of age receiving bivalent rLP2086 or bivalent rLP2086-containing vaccines (MenABCWY) and have not been observed in infants 6 months or older, nor individuals receiving Nimenrix without bivalent rLP2086. No safety concerns were identified in relation to Nimenrix.

Only objectives relating to the safety and immunogenicity of Nimenrix will be described in this report.

Table 1: Treatment Groups for Open-Label Sentinel-Cohort and Expanded Enrolment Stages

Cohort	Group	Intervention (s)	Age	Enrollment Status[a]	Vaccinations Administered[b]
Sentinel Cohort 1	Group 1	MenABCWY + PLP	6-Month-Old	Completed	Vaccination 1 Vaccination 2 Booster Vaccination
Sentinel Cohort 2	Group 2	MenABCWY		Completed	
	Group 3	60 µg rLP2086 + Nimenrix + PLP/SLP	2-Month-Old	Completed	
Sentinel Cohort 3	Group 4	60 µg rLP2086 + Nimenrix		Not Completed[c]	
	Group 5	120 µg rLP2086 + Nimenrix + PLP		Completed	
Sentinel Cohort 4	Group 7	MenABCWY + SLP		Completed	Vaccination 1 Vaccination 2
Sentinel-Control Cohort	Group 8	Bexsero + Nimenrix + PLP		Completed	Vaccination 1 Vaccination 2 Booster Vaccination
	Group 10	Bexsero + Nimenrix		Completed	
Open-Label Expanded-Enrollment Stage	Group 11	MenABCWY + TLP		Not Completed	Vaccination 1

a. The study did not progress to the blinded expanded-enrollment stage and no participants were enrolled in Group 13 (MenABCWY + placebo + SLP or TLP) or Group 14 (Bexsero+ Nimenrix + PLP or TLP).

b. Participants 6 months of age (Groups 1 and 2) received Prevenar 13 and Vaxelis concomitantly with Vaccination 1. Participants 2 months of age (Groups 3-5, 7, 8 and 10) received Prevenar 13 and Vaxelis at 2 and 4 months of age concomitantly with Vaccination 1 and 2 respectively.
c. This is based on a recommendation from the IRC and EDMC that no further participants be enrolled into Group 4 which did not contain any protocol-assigned paracetamol regimen as part of the study intervention.
PLP = prophylactic liquid paracetamol regimen (consisted of 3 required doses of paracetamol with the first dose starting 30 minutes before vaccination and 2 additional doses administered every 4-6 hours).
SLP = scheduled liquid paracetamol regimen (consisted of an initial dosing schedule of 4 or 5 paracetamol doses that started no later than 8 hours after vaccination).
TLP = therapeutic liquid paracetamol regimen (consisted of an initial dosing schedule of 4 or 5 paracetamol doses given as treatment only when fever or other reactogenicity symptoms arose within 48 hours after the primary series vaccinations and required treatment [if no symptoms were experienced, no paracetamol was given])

Methods

Study participants

Up to 1272 participants were planned to be enrolled, with approximately up to 472 participants in the open-label stages and up to 800 in the blinded expanded-enrolment stage.

Treatments and immunisation schedule

Trumenba (Bivalent rLP2086), Bexsero and MenACWY-TT (Nimenrix).

Primary vaccination involved two immunisations two months apart ('Vaccination 1' and 'Vaccination 2'). Immunogenicity was determined one month after completion of primary vaccination (i.e., Vaccination 2).

A booster vaccination would be given 10 months after the second vaccination (Vaccination 2) for those aged two months which includes groups 7, 8 + 10 described in this report (**Table *1***). Immunogenicity was assessed one month after the booster immunisation.

Assessors comment:

Primary vaccination: The immunisation regimen is in line with the SmPC for Nimenrix and Bexsero for this age group. However, the Trumenba posology for primary vaccination two dose regimen is two doses 6 months apart for the age group ≥10 years. A three-dose regimen for Trumenba (months 0, 2 and 6) has also been approved in children and adults >10 years of age. The immunisation regimen for the combined product MenABCWY is therefore not fully in accordance with the current Trumenba posology for the older age group for which the product is currently approved.

Booster immunisation: According to the SmPC for Nimenrix, a booster dose should be given at age 12 months and at least two months after the last Nimenrix vaccination. For Bexsero a boost may be given in the age group 2 months to 5 months to infants between 12 and 15 months of age at least 6 months following the last immunisation. Booster doses for Trumenba have been given as early as two years after primary vaccination of children 3 to 5 years of age. Booster doses have also been given 4 years post primary vaccination of 4-year-old children. The booster schedule for MenABCWY in this clinical study is therefore not consistent with the SmPC for Trumenba.

Objectives and endpoints relating to Nimenrix

Primary immunogenicity objective:

The primary immunogenicity objectives and endpoints relating to Nimenrix are shown in **Table *2***.

Table 2: Primary Objectives, Estimands, and Endpoints for the Open-Label Sentinel-Cohort and Expanded-Enrollment Stages

Planned Objectives, Estimands, and Endpoints			Objectives, Estimands, and Endpoints Impacted by Study Termination
Objectives	**Estimands**	**Endpoints**	**Reference**
Primary Immunogenicity:	Primary Immunogenicity:	Primary Immunogenicity:	
To describe the immune response for MenA, MenC, MenW, and MenY induced by MenABCWY compared to the immune response induced by Nimenrix after 2 primary vaccinations and after a booster dose.	In participants receiving primary vaccinations 1 and 2, who are in compliance with the key protocol criteria (evaluable participants), expressed in the following group combinations: Groups 7+11 (MenABCWY recipients) Groups 8+10 (Nimenrix recipients) The percentage of participants achieving an hSBA titer ≥ LLOQ for each MenA, MenC, MenW, and MenY test strain 1 month after primary vaccination 2. In participants who completed primary vaccinations and received a booster dose, and who are in compliance with the key protocol criteria (evaluable participants), expressed in the same group combinations as above: The percentage of participants achieving an hSBA titer ≥ LLOQ for each MenA, MenC, MenW, and MenY test strain 1 month after the booster vaccination.	hSBA titer for each of the MenA, MenC, MenW, and MenY test strains.	The immune response following 2 primary vaccinations is not reported for Group 11. The immune response following booster vaccination is not reported for Groups 7+11.

Secondary immunogenicity objectives

There were no secondary immunogenicity objectives relating to Nimenrix in this study.

Exploratory immunogenicity objectives

Exploratory immunogenicity objectives and endpoints are shown in **Table *3***.

Table 3: Tertiary/Exploratory Immunogenicity Objectives, Estimands, and Endpoints for the Open-Label Sentinel-Cohort and Expanded-Enrollment Stages

Planned Objectives, Estimands, and Endpoints			Objectives, Estimands, and Endpoints Impacted by Study Termination
Objectives	**Estimands**	**Endpoints**	**Reference**
To further describe the immune response for MenA, MenC, MenW, and MenY induced by MenABCWY compared to the immune response induced by Nimenrix after 2 primary vaccinations and after a booster dose.	In participants receiving primary vaccinations 1 and 2, who are in compliance with the key protocol criteria (evaluable participants), expressed in the following group combinations: Groups 7+11 (MenABCWY recipients) Groups 8+10 (Nimenrix recipients) hSBA GMTs for each of the MenA, MenC, MenW, and MenY test strains 1 month after primary vaccination 2. In participants who completed primary vaccinations and received a booster dose, and who are in compliance with the key protocol criteria (evaluable participants), expressed in the same group combinations as above: hSBA GMTs for each of the MenA, MenC, MenW, and MenY test strains 1 month after the booster vaccination.	hSBA titer for each of the MenA, MenC, MenW, and MenY test strains.	Vaccination 2 was not administered to participants in Group 11 and therefore, the immune response following primary vaccinations is not reported. The booster dose was not administered to participants in Group 11 and therefore, post-booster immune response is not reported.
To describe the immune response for MenA, MenC, MenW, and MenY induced by 2 doses of MenABCWY compared to the immune response induced by 2 doses of Nimenrix, by protocol-assigned paracetamol regimen.	In participants receiving primary vaccinations 1 and 2, who are in compliance with the key protocol criteria (evaluable participants), expressed by protocol-assigned paracetamol regimen and irrespective of protocol-assigned paracetamol regimen receipt, in the following group combinations: Groups 7+11 (MenABCWY recipients with SLP or TLP) Groups 8+10 (Nimenrix recipients with or without PLP) The percentage of participants achieving an hSBA titer ≥ LLOQ for each of the MenA, MenC, MenW, and MenY test strains 1 month after primary vaccination 2.	hSBA titer for each of the MenA, MenC, MenW, and MenY test strains.	Vaccination 2 was not administered to participants in Group 11 and therefore, the immune response following primary vaccinations is not reported.
To describe the immune response for MenA, MenC, MenW, and MenY induced by MenABCWY after 2 primary vaccinations and after a booster dose in healthy infants 6 months of age at study entry.	In participants receiving primary vaccinations 1 and 2, who are in compliance with the key protocol criteria (evaluable participants), expressed in the following group combination: Groups 1+2 (MenABCWY recipients) The percentage of participants achieving an hSBA titer ≥ LLOQ for each MenA, MenC, MenW, and MenY test strain 1 month after primary vaccination 2. hSBA GMTs for each of the MenA, MenC, MenW, and MenY test strains 1 month after primary vaccination 2. In participants who completed primary vaccinations and received a booster dose, and who are in compliance with the key protocol criteria (evaluable participants), expressed in the same group combination as above: The percentage of participants achieving an hSBA titer ≥ LLOQ for each MenA, MenC, MenW, and MenY test strain 1 month after the booster vaccination. hSBA GMTs for each of the MenA, MenC, MenW, and MenY test strains 1 month after the booster vaccination.	hSBA titer for each of the MenA, MenC, MenW, and MenY test strains.	Immunogenicity data for Group 1 and Group 2 are not reported in this CSR and may be reported in a future supplemental report.

Sample size

The sample size for the open-label sentinel-cohort and the expanded-enrolment stages was not based on any hypothesis-testing criteria. The study aimed to have a sufficient number of participants in order to describe safety and the immunogenicity. With 150 enrolled participants in Groups 7+11 combined, the ratio of the lower bound of the one-sample 95% CI for the GMT to the GMT is approximately 0.76 and 0.66, respectively, for an assumed maximum SD of 1.3 for MenB test strains and 2.0 for MenA, MenC, MenW, and MenY test strains, assuming that 70% of the participants will have test results for all the strains and a 15% exclusion rate from the (post–primary vaccination 2) evaluable population. With a similar assumption and 110 enrolled participants in Groups 8+10 combined, the ratio of the lower bound of the one sample 95% CI for the GMT to the GMT is approximately 0.73 and 0.62, respectively.

Randomisation and blinding (masking)

Allocation (randomisation) of participants to vaccine groups was carried out using an IRT system (IWR) that was accessible 24 hours a day, 365 days a year. The site personnel (study coordinator or specified designee) were required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel would then be provided with a vaccine assignment, randomisation number, and DU or container number when study intervention was being supplied via the IRT system. The IRT system provided a confirmation report containing the participant number, randomisation number, and DU or container number assigned. The randomisation number and the date on which the randomisation number was assigned was recorded on the CRF. The confirmation report must be stored in the site's files.

The study specific IRT reference manual and IP manual provided the contact information and further details on the use of the IRT system.

During both the open-label and blinded stages, the specific study intervention dispensed to the participant was assigned using an IRT. The site contacted the IRT prior to the start of study intervention administration for each participant. The site recorded the study intervention assignment on the applicable CRF, if required.

During the open-label stages, the investigator's knowledge of the vaccine assignment should not influence the decision to enrol a particular participant or affect the order in which participants are enrolled.

All study staff and sponsor personnel will be unblinded during the open-label stages.

Statistical Methods

This was not a hypothesis-testing study; an estimation approach was used to assess the immunogenicity and safety objectives in the study. All immunogenicity data was summarised descriptively. For all binary endpoints (including primary endpoints), counts, percentages, and 2-sided 95% CIs using the Clopper-Pearson method was calculated. For hSBA titer results, geometric means and 2-sided 95% CIs based on the t-distribution was computed.

The primary immunogenicity objectives were evaluated by descriptive summary statistics for the percentages of participants achieving hSBA titers $\geq$ LLOQ 1 month after primary vaccination 2 and 1 month after the booster vaccination. Additionally, hSBA GMTs and the RCDCs of the hSBA titers were to be provided for the specified time points to provide further characterization of the immune response.

The primary safety objective was evaluated by descriptive summary statistics for local reactions, systemic events, and AEs, including SAEs, MAEs, and NDCMCs.

Results

Participant flow

The study was designed to be conducted in 3 stages: an open-label sentinel-cohort stage, an open-label expanded-enrolment stage, and a blinded expanded-enrolment stage. For sentinel Cohorts 1 to 4 (see **Table *1***), enrolment was initiated in each cohort sequentially, starting with Cohort 1. Enrolment in each of these cohorts, as well as in the open-label expanded-enrolment stage, was restricted to 3 participants per day until the first 9 participants had been enrolled. Progression to the subsequent cohort as well as progression to the open-label expanded-enrolment stage occurred only after the IRC had reviewed data from previous cohort(s) and found the safety profile acceptable.

As a result of early study termination, the study did not complete as originally intended and the majority of participants did not complete the study. Consequently, the most common reason overall for withdrawal during the study was study termination by sponsor.

Recruitment

First participant first visit: 26 November 2020 (study start).

The study was terminated early on 17 March 2022.

Last participant last visit: 15 September 2022.

A total of 326 participants were enrolled at 32 centres in 4 countries: Spain, Greece, Germany, and Romania.

Demographics and baseline data

Most participants were White (range, 87.0% to 100%), followed by 2.8% to 4.3% of participants who were Black or African American, and 1.9% to 8.7% of participants with race not reported. There were 18.9% to 58.3% of participants who were Hispanic/Latino. The proportion of participants who were male ranged from 41.7% to 63.6%. The median age at the first vaccination for participants who were 6 months old (Group 1 and Group 2) was 156.0 days, and the median age for participants who were 2 months old (all other groups) was 64.0 to 71.0 days.

Demographic characteristics are presented in **Table *4***.

Table 4. Demographic Characteristics – Safety Population

	Vaccine Group (as Administered)								
	Sentinel Cohort 1	Sentinel Cohort 2		Sentinel Cohort 3		Sentinel Cohort 4	Sentinel-Control Cohort		Open-Label Expanded-Enrollment Stage
	Group 1 (6 Mo) MenABCWY +PLP (N^a=23) n^b (%)	Group 2 (6 Mo) MenABCWY (N^a=25) n^b (%)	Group 3 (2 Mo) 60 µg rLP2086 +Nimenrix +PLP/SLP (N^a=36) n^b (%)	Group 4 (2 Mo) 60 µg rLP2086 +Nimenrix (N^a=16) n^b (%)	Group 5 (2 Mo) 120 µg rLP2086 +Nimenrix +PLP (N^a=53) n^b (%)	Group 7 (2 Mo) MenABCWY +SLP (N^a=50) n^b (%)	Group 8 (2 Mo) Bexsero +Nimenrix +PLP (N^a=55) n^b (%)	Group 10 (2 Mo) Bexsero +Nimenrix (N^a=55) n^b (%)	Group 11 (2 Mo) MenABCWY +TLP (N^a=12) n^b (%)
Sex									
Male	11 (47.8)	15 (60.0)	15 (41.7)	9 (56.3)	29 (54.7)	23 (46.0)	23 (41.8)	35 (63.6)	5 (41.7)
Female	12 (52.2)	10 (40.0)	21 (58.3)	7 (43.8)	24 (45.3)	27 (54.0)	32 (58.2)	20 (36.4)	7 (58.3)
Race									
White	20 (87.0)	24 (96.0)	35 (97.2)	16 (100.0)	52 (98.1)	50 (100.0)	55 (100.0)	55 (100.0)	12 (100.0)
Black or African American	1 (4.3)	1 (4.0)	1 (2.8)	0	0	0	0	0	0
Asian	0	0	0	0	0	0	0	0	0
Unknown	0	0	0	0	0	0	0	0	0
Multiracial	0	0	0	0	0	0	0	0	0
Not reported	2 (8.7)	0	0	0	1 (1.9)	0	0	0	0
Ethnicity									
Hispanic or Latino	13 (56.5)	9 (36.0)	21 (58.3)	8 (50.0)	10 (18.9)	25 (50.0)	18 (32.7)	22 (40.0)	6 (50.0)
Non-Hispanic/non-Latino	10 (43.5)	16 (64.0)	15 (41.7)	8 (50.0)	43 (81.1)	25 (50.0)	37 (67.3)	33 (60.0)	6 (50.0)
Not reported	0	0	0	0	0	0	0	0	0
Age at first vaccination (days)									
Mean (SD)	158.5 (6.87)	161.6 (14.45)	71.1 (7.00)	67.6 (5.81)	68.9 (6.39)	68.0 (5.99)	67.4 (7.89)	67.5 (7.30)	69.4 (7.69)
Median	156.0	156.0	71.0	65.5	67.0	66.0	64.0	64.0	65.5
Min, max	(151, 176)	(151, 208)	(62, 88)	(61, 79)	(62, 90)	(61, 85)	(61, 97)	(61, 92)	(62, 84)

Numbers analysed

The numbers analysed are shown in **Table *5***.

Table 5. Immunogenicity Populations by Group

	Vaccine Group (as Randomized)					
	Sentinel Cohort 2	Sentinel Cohort 3		Sentinel Cohort 4	Sentinel-Control Cohort	
	Group 3 (2 Mo) 60 µg rLP2086 +Nimenrix +PLP/SLP n[a] (%)	Group 4 (2 Mo) 60 µg rLP2086 +Nimenrix n[a] (%)	Group 5 (2 Mo) 120 µg rLP2086 +Nimenrix +PLP n[a] (%)	Group 7 (2 Mo) MenABCWY +SLP n[a] (%)	Group 8 (2 Mo) Bexsero +Nimenrix +PLP n[a] (%)	Group 10 (2 Mo) Bexsero +Nimenrix n[a] (%)
Randomized[b]	39	17	50	50	55	55
Post–Primary Vaccination 2 mITT population	23 (59.0)	15 (88.2)	50 (100.0)	20 (40.0)	54 (98.2)	54 (98.2)
Excluded from post–Primary Vaccination 2 mITT population	16 (41.0)	2 (11.8)	0	30 (60.0)	1 (1.8)	1 (1.8)
Post–Primary Vaccination 2 evaluable immunogenicity population	21 (53.8)	14 (82.4)	45 (90.0)	18 (36.0)	49 (89.1)	48 (87.3)
Excluded from post–Primary Vaccination 2 evaluable immunogenicity population	18 (46.2)	3 (17.6)	5 (10.0)	32 (64.0)	6 (10.9)	7 (12.7)
Reason for exclusion						
Did not maintain eligibility based on criteria up until and including Visit 4	16 (41.0)	1 (5.9)	0	14 (28.0)	1 (1.8)	0
Did not receive study intervention at Visits 1 and 3 as randomized	18 (46.2)	1 (5.9)	0	8 (16.0)	1 (1.8)	0
Did not have blood draw within 28 to 42 days after vaccination at Visit 4	16 (41.0)	1 (5.9)	2 (4.0)	30 (60.0)	6 (10.9)	6 (10.9)
Did not have valid and determinate MenACWY or MenB assay result at Visit 4	16 (41.0)	2 (11.8)	0	30 (60.0)	1 (1.8)	1 (1.8)
Received prohibited vaccines or treatment	0	0	1 (2.0)	1 (2.0)	0	0
Had important protocol deviations	3 (7.7)	1 (5.9)	3 (6.0)	2 (4.0)	0	1 (1.8)
Post–booster vaccination mITT population	21 (53.8)	0	0	0	23 (41.8)	22 (40.0)
Excluded from post–booster vaccination mITT population	18 (46.2)	17 (100.0)	50 (100.0)	50 (100.0)	32 (58.2)	33 (60.0)
Post–booster vaccination evaluable immunogenicity population	18 (46.2)	0	0	0	23 (41.8)	20 (36.4)
Excluded from post–booster vaccination evaluable immunogenicity population	21 (53.8)	17 (100.0)	50 (100.0)	50 (100.0)	32 (58.2)	35 (63.6)
Reason for exclusion						
Did not maintain eligibility based on criteria up until and including Visit 6	18 (46.2)	14 (82.4)	42 (84.0)	50 (100.0)	13 (23.6)	14 (25.5)
Did not receive study intervention at Visits 1, 3 and 5 as randomized	19 (48.7)	13 (76.5)	41 (82.0)	50 (100.0)	8 (14.5)	10 (18.2)
Did not have blood draw within 28 to 42 days after vaccination at Visit 6	19 (48.7)	17 (100.0)	50 (100.0)	50 (100.0)	31 (56.4)	34 (61.8)
Did not have a valid and determinate MenACWY or MenB assay result at Visit 6	18 (46.2)	17 (100.0)	50 (100.0)	50 (100.0)	32 (58.2)	33 (60.0)
Received prohibited vaccines or treatment	0	0	0	0	0	0
Had important protocol deviations	3 (7.7)	0	3 (6.0)	0	0	1 (1.8)

Abbreviations: Mo = months of age; mITT = modified intent-to-treat; PLP = prophylactic liquid paracetamol; SLP = scheduled liquid paracetamol.
Note: Immunogenicity endpoints (tertiary/exploratory) for Groups 1 and 2 are not reported in the CSR.
Note: The participants randomized into Group 11 had no serum samples collected for serology testing due to study termination.
Note: No participants were enrolled into Group 13 and Group 14 due to study termination.
a. n = Number of participants with the specified characteristic.
b. The values in this row are used as the denominators for percentage calculations.

The most common reason for exclusion for the immunogenicity populations were related to study termination.

Efficacy results

Efficacy results are only available for groups 7, 8 and 10. These groups recruited participants aged 2 months. No data has been submitted for groups 1 and 2 recruiting participants aged 6 months.

Primary Immunogenicity objective

The primary immunogenicity objective relating to Nimenrix was to describe the immune response for MenA, MenC, MenW, and MenY induced by MenABCWY (Group 7) compared to the immune response induced by Nimenrix and Bexsero (Group 8 with prophylactic liquid paracetamol (PLP) and Group 10 without PLP) after 2 primary vaccinations and after a booster dose based on hSBA titres for each of the MenA, MenC, MenW and MenY test strains.

For the post-Primary Vaccination 2 evaluable immunogenicity population, 100% of the participants in the MenABCWY + scheduled liquid paracetamol (SLP) group (Group 7) and the Bexsero + Nimenrix (with/without PLP) groups (Groups 8 and 10) achieved an hSBA titer ≥ LLOQ at 1 month after Primary Vaccination 2 for the 4 serogroups (MenA, MenC, MenW, and MenY) (**Table *6***).

Table 6: Number (%) of participants with hSBA titre >LLOQ for MenA, MenC, MenW, and MenY Test strains 1 month after primary vaccination 2 – post-primary vaccination 2 evaluable immunogenicity population – Primary endpoint

	Vaccine Group (as Randomized)		
	Group 7 (2 Mo) MenABCWY + SLP	Group 8 (2 Mo) Bexsero + Nimenrix + PLP	Group 10 (2 Mo) Bexsero + Nimenrix
Serogroup	N[a] n[b] (%) (95% CI[c])	N[a] n[b] (%) (95% CI[c])	N[a] n[b] (%) (95% CI[c])
MenA	16 16 (100.0) (79.4, 100.0)	43 43 (100.0) (91.8, 100.0)	47 47 (100.0) (92.5, 100.0)
MenC	16 16 (100.0) (79.4, 100.0)	45 45 (100.0) (92.1, 100.0)	46 46 (100.0) (92.3, 100.0)
MenW	16 16 (100.0) (79.4, 100.0)	44 44 (100.0) (92.0, 100.0)	47 47 (100.0) (92.5, 100.0)
MenY	16 16 (100.0) (79.4, 100.0)	45 45 (100.0) (92.1, 100.0)	47 47 (100.0) (92.5, 100.0)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; MenA, MenC, MenW, and MenY = *Neisseria meningitidis* group A, group C, group W, and group Y; Mo = months of age.
Note: LLOQ = 1:8 for MenA, MenC, MenW, and MenY serogroups.
Note: The protocol immunogenicity assessment did not include evaluation of MenA, MenC, MenW, and MenY serogroups in Groups 3, 4, and 5.
Note: The participants randomized into Group 11 had no serum samples collected for serology testing due to study termination.
Note: No participants were enrolled into Group 13 and Group 14 due to study termination.
a. N = number of participants with valid and determinate hSBA titers for the given strain from those that had, 1 month after vaccination, 2 blood sample collections.
b. n = Number of participants with observed hSBA titer ≥ LLOQ for the given strain from those that had, 1 month after vaccination, 2 blood sample collections.
c. Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.

As a result of early study termination, participants in Group 7 did not receive a booster dose.

For the post-booster vaccination evaluable immunogenicity population, 100% of all participants in Groups 8 and 0 achieved an hSBA titer ≥ LLOQ at 1 month after booster vaccination for the 4 serogroups (MenA, MenC, MenW, and MenY) (**Table *7***).

Table 7: Number (%) of participants with hSBA titre >LLOQ for MenA, MenC, MenW, and MenY Test strains 1 month after booster vaccination – post-booster vaccination evaluable immunogenicity population – Primary Endpoint

Serogroup	Vaccine Group (as Randomized) Groups 8 + 10 (2 Mo) Bexsero + Nimenrix (With/Without PLP) N[a] n[b] (%) (95% CI[c])
MenA	41 41 (100.0) (91.4, 100.0)
MenC	41 41 (100.0) (91.4, 100.0)
MenW	42 42 (100.0) (91.6, 100.0)
MenY	41 41 (100.0) (91.4, 100.0)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; MenA, MenC, MenW, and MenY = *Neisseria meningitidis* group A, group C, group W, and group Y; Mo = months of age.
Note: LLOQ = 1:8 for MenA, MenC, MenW, and MenY serogroups.
Note: The protocol immunogenicity assessment did not include evaluation of MenA, MenC, MenW, and MenY serogroups in Groups 3, 4, and 5.
Note: The participants randomized into Group 11 had no serum samples collected for serology testing due to study termination.
Note: The participants randomized into Group 7 had no serum samples collected post-booster for serology testing due to study termination.
Note: No participants were enrolled into Group 13 and Group 14 due to study termination.
a. N = number of participants with valid and determinate hSBA titers for the given strain from those that had, 1 month after vaccination, 2 blood sample collections.
b. n = Number of participants with observed hSBA titer ≥ LLOQ for the given strain from those that had, 1 month after vaccination, 2 blood sample collections.
c. Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method

Secondary Immunogenicity objectives

There were no secondary immunogenicity objectives relating to Nimenrix.

Tertiary immunogenicity objectives

Tertiary/Exploratory Immunogenicity objectives were to further describe the immune response to MenA, MenC, MenW, and MenY induced by MenABCWY compared to the immune response induced by Nimenrix after 2 primary vaccinations and after a booster dose, shown as hSBA titres for each of the MenA, MenC, MenW and MenY test strains. Group 1 and Group 2 are not reported due to lack of available sera since this was used primarily for assay development based on an amendment to the protocol (Amendment 1).

hSBA GMTs for MenA, MenC, MenW, and MenY test strains 1 month after Primary Vaccination 2 ranged from 124.2 to 921.5 (**Table *8***) and substantially increased for all 4 serogroups 1 month after booster vaccination, ranging from 557.2 to 3,343.9 (**Table *9***).

Table 8: bSBA GMTs for MenA, MenC, MenW, and MenY Test strains 1 month after primary vaccination 2 – post-primary vaccination 2 Evaluable Immunogenicity population – Tertiary Endpoint.

	Vaccine Group (as Randomized)	
	Group 7 (2 Mo) MenABCWY + SLP	Groups 8 + 10 (2 Mo) Bexsero + Nimenrix (With/Without PLP)
Serogroup	N[a] GMT[b] (95% CI[c])	N[a] GMT[b] (95% CI[c])
MenA	16 189.0 (132.4, 269.9)	90 183.8 (156.6, 215.8)
MenC	16 145.8 (76.1, 279.2)	91 140.3 (118.8, 165.5)
MenW	16 317.9 (218.6, 462.4)	91 124.2 (105.3, 146.5)
MenY	16 583.1 (416.5, 816.2)	92 921.5 (825.1, 1029.1)

Abbreviations: GMT = geometric mean titer; hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; MenA, MenC, MenW, and MenY = *Neisseria meningitidis* group A, group C, group W, and group Y; Mo = months of age.
Note: LLOQ = 1:8 for MenA, MenC, MenW, and MenY serogroups.
Note: If the hSBA result is below LLOQ, it will be set to 0.5 × LLOQ for the GMT calculation.
Note: Immunogenicity endpoints (tertiary/exploratory) for Groups 1 and 2 are not reported in the CSR.
Note: The protocol immunogenicity assessment did not include evaluation of MenA, MenC, MenW, and MenY serogroups in Groups 3, 4, and 5.
Note: The participants randomized into Group 11 had no serum samples collected for serology testing due to study termination.
Note: No participants were enrolled into Group 13 and Group 14 due to study termination.
a. N = number of participants with valid and determinate hSBA titers for the given strain from those that had, 1 month after vaccination, 2 blood sample collections.
b. GMTs are calculated using all participants with valid and determinate hSBA titers from those that had, 1 month after vaccination, 2 blood sample collections by exponentiating the mean logarithm of the titers.
c. CIs are calculated by exponentiating the confidence limits based on the Student t distribution for the mean logarithm of the titers.

Table 9: hSBA GMTs for for MenA, MenC, MenW, and MenY Test strains 1 month after Booster vaccination – Post-Booster Vaccination Evaluable Immunogenicity population – Tertiary Endpoint.

	Vaccine Group (as Randomized)
	Groups 8 + 10 (2 Mo) Bexsero + Nimenrix (With/Without PLP)
Serogroup	N[a] GMT[b] (95% CI[c])
MenA	41 718.0 (559.1, 921.9)
MenC	41 557.2 (425.8, 729.0)
MenW	42 677.8 (501.2, 916.7)
MenY	41 3343.9 (2683.2, 4167.2)

Abbreviations: GMT = geometric mean titer; hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; MenA, MenC, MenW, and MenY = *Neisseria meningitidis* group A, group C, group W, and group Y; Mo = months of age.
Note: LLOQ = 1:8 for MenA, MenC, MenW, and MenY serogroups.
Note: If the hSBA result is below LLOQ, it will be set to 0.5 × LLOQ for the GMT calculation.
Note: Immunogenicity endpoints (tertiary/exploratory) for Groups 1 and 2 are not reported in the CSR.
Note: The protocol immunogenicity assessment did not include evaluation of MenA, MenC, MenW, and MenY serogroups in Groups 3, 4, and 5.

Note: The participants randomized into Group 7 had no serum samples collected post-booster for serology testing due to study termination.
Note: The participants randomized into Group 11 had no serum samples collected for serology testing due to study termination.
Note: No participants were enrolled into Group 13 and Group 14 due to study termination.
a. N = number of participants with valid and determinate hSBA titers for the given strain from those that had, 1 month after vaccination, 2 blood sample collections.
b. GMTs are calculated using all participants with valid and determinate hSBA titers from those that had, 1 month after vaccination, 2 blood sample collections by exponentiating the mean logarithm of the titers.
c. CIs are calculated by exponentiating the confidence limits based on the Student t distribution for the mean logarithm of the titers.

Reverse cumulative distribution curves showing the distribution of hSBA titres for MenA, MenC, MenW and Men Y suggest that for the majority of participants who received MenABCWY + SLP (Group 7) and Bexsero + Nimenrix (with/without PLP) (Groups 8 + 10) responded 1 month after Vaccination 2 (**Figure *1***). The titres to the different serogroups were largely overlapping between MenABCWY and Nimenrix for MenA, MenC, and MenY antigens with the exception of MenW where the titres were slightly lower for MenACWY compared to MenABCWY following primary vaccination.

Only groups 8 + 10 received booster immunisation. This was shown to increase the titres substantially towards these antigens consistent with an anamnestic immune response (**Figure *1***).

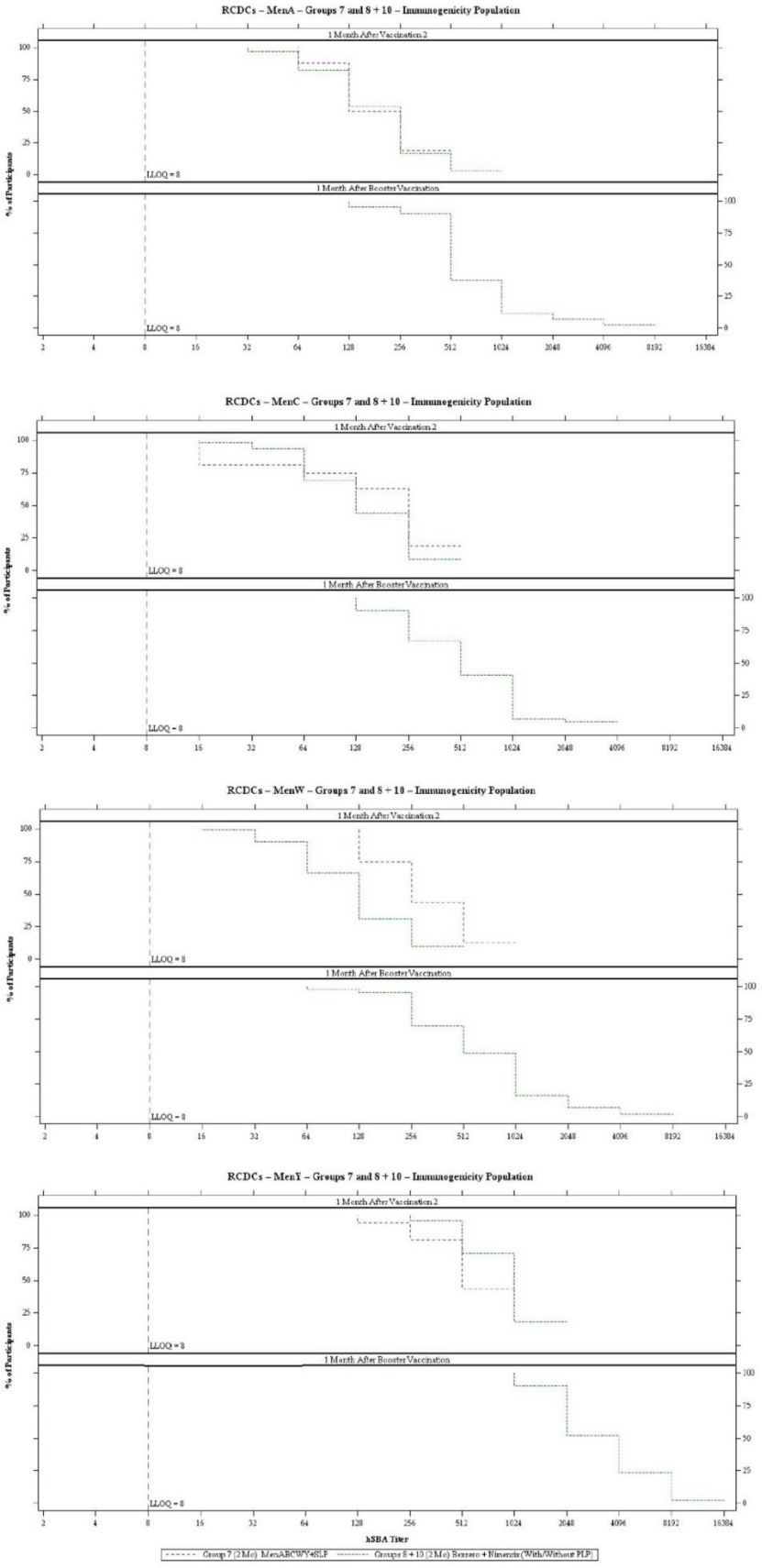

Figure 1: RDCDs for MenA, MenC, MenW and MenY – Groups 7 and 8 + 10 – Immunogenicity population.

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; MenY = Neisseria meningitis serotype Y, MenA = Neisseria meningitis serotype A; MenC = Neisseria meningitis serotype C; MenW = Neisseria meningitis serotype W-135.
Note: Include those who met post-primary Vaccination 2 evaluable immunogenicity population of post-booster Vaccination evaluable immunogenicity population.
Note: No participants that were randomised into group 7 and 11 received booster vaccination prior to study termination.

Safety results

This study was terminated on 17 March 2022 after a review of all safety data by the MAH, including 2 cases of CSF pleocytosis that occurred in this study in 2-month-old infants receiving either bivalent rLP2086 associated with Nimenrix or MenABCWY, and a third case of CSF pleocytosis after administration of bivalent rLP2086 in another early terminated study (study B1971008). As a result, all active participants were permanently discontinued from further study vaccinations or blood draws and participants were followed up for safety for up to 6 months from their last study vaccination. The majority of participants did not complete the study as planned. Study subjects in group 11 (MenABCWY + TLP) had only received one primary vaccination at study termination and did consequently not receive a second primary or booster vaccination. Group 7 (MenABCWY + SLP) did not receive a booster vaccination of MenABCWY.
The overall safety population included a total of 325 participants across all vaccine groups and all participants were included in the Primary Vaccination 1 safety population (**Table *10***).

Assessors comment:

The majority of safety analysis and tables presented by the MAH are comparisons between MenABCWY + SLP/TLP (Groups 7+11) and Bexsero + Nimenrix (with/without PLP) (Groups 8+10). Also, no joint analysis of all data from groups receiving different combinations of Nimenrix and Trumenba (group 1-7 +11) has been presented. No clear explanation for this has been provided, however, as it would not change the outcome of the assessment regarding Nimenrix, a clarification is not requested.

Table 10: Safety population by group

	Vaccine Group (as Administered)								
	Sentinel Cohort 1	Sentinel Cohort 2		Sentinel Cohort 3		Sentinel Cohort 4	Sentinel-Control Cohort		Open-Label Expanded-Enrollment Stage
	Group 1 (6 Mo) MenABCWY +PLP n[a] (%)	Group 2 (6 Mo) MenABCWY n[a] (%)	Group 3 (2 Mo) 60 µg rLP2086 +Nimenrix +PLP/SLP n[a] (%)	Group 4 (2 Mo) 60 µg rLP2086 +Nimenrix n[a] (%)	Group 5 (2 Mo) 120 µg rLP2086 +Nimenrix +PLP n[a] (%)	Group 7 (2 Mo) MenABCWY +SLP n[a] (%)	Group 8 (2 Mo) Bexsero +Nimenrix +PLP n[a] (%)	Group 10 (2 Mo) Bexsero +Nimenrix n[a] (%)	Group 11 (2 Mo) MenABCWY +TLP n[a] (%)
Not vaccinated[b]	0	0	0	1	0	0	0	0	0
Vaccine administered[c]	23	25	36	16	53	50	55	55	12
Safety population	23 (100.0)	25 (100.0)	36 (100.0)	16 (100.0)	53 (100.0)	50 (100.0)	55 (100.0)	55 (100.0)	12 (100.0)
Excluded from safety population	0	0	0	0	0	0	0	0	0
Did not have safety information	0	0	0	0	0	0	0	0	0
Primary Vaccination 1 safety population	23 (100.0)	25 (100.0)	36 (100.0)	16 (100.0)	53 (100.0)	50 (100.0)	55 (100.0)	55 (100.0)	12 (100.0)
Excluded from Primary Vaccination 1 safety population	0	0	0	0	0	0	0	0	0
No study vaccination was received	0	0	0	0	0	0	0	0	0
Did not have safety information from Visit 1 to prior to Visit 3	0	0	0	0	0	0	0	0	0
Primary Vaccination 2 safety population	22 (95.7)	25 (100.0)	21 (58.3)	16 (100.0)	52 (98.1)	42 (84.0)	54 (98.2)	55 (100.0)	0

Excluded from Primary Vaccination 2 safety population	1 (4.3)	0	15 (41.7)	0	1 (1.9)	8 (16.0)	1 (1.8)	0	12 (100.0)
No study vaccination was received	1 (4.3)	0	15 (41.7)	0	1 (1.9)	8 (16.0)	1 (1.8)	0	12 (100.0)
Did not have safety information from Visit 3 to prior to Visit 4	0	0	0	0	0	0	0	0	0
Primary Vaccination 2 follow-up safety population	22 (95.7)	25 (100.0)	21 (58.3)	16 (100.0)	52 (98.1)	41 (82.0)	54 (98.2)	55 (100.0)	0
Excluded from Primary Vaccination 2 follow-up safety population	1 (4.3)	0	15 (41.7)	0	1 (1.9)	9 (18.0)	1 (1.8)	0	12 (100.0)
Did not have safety information from Visit 4 to prior to Visit 5	1 (4.3)	0	15 (41.7)	0	1 (1.9)	9 (18.0)	1 (1.8)	0	12 (100.0)
Booster vaccination safety population	22 (95.7)	25 (100.0)	20 (55.6)	4 (25.0)	11 (20.8)	0	47 (85.5)	45 (81.8)	0
Excluded from booster vaccination safety population	1 (4.3)	0	16 (44.4)	12 (75.0)	42 (79.2)	50 (100.0)	8 (14.5)	10 (18.2)	12 (100.0)
No study vaccination was received	1 (4.3)	0	16 (44.4)	12 (75.0)	42 (79.2)	50 (100.0)	8 (14.5)	10 (18.2)	12 (100.0)
Did not have safety information from Visit 5 to prior to Visit 6	0	0	0	0	0	0	0	0	0
Booster vaccination follow-up safety population	22 (95.7)	25 (100.0)	20 (55.6)	4 (25.0)	11 (20.8)	0	47 (85.5)	45 (81.8)	0
Excluded from booster vaccination follow-up safety population	1 (4.3)	0	16 (44.4)	12 (75.0)	42 (79.2)	50 (100.0)	8 (14.5)	10 (18.2)	12 (100.0)
Did not have safety information from Visit 6 to prior to Visit 7	1 (4.3)	0	16 (44.4)	12 (75.0)	42 (79.2)	50 (100.0)	8 (14.5)	10 (18.2)	12 (100.0)

Abbreviation: Mo = months of age; PLP = prophylactic liquid paracetamol; SLP = scheduled liquid paracetamol; TLP = therapeutic liquid paracetamol.
Note: Three participants in Group 3 received 120 µg instead of 60 µg rLP2086 as result of a medication error that occurred at Vaccination 1 and were included in Group 5 for reporting.
Note: No participants were enrolled into Group 13 and Group 14 due to study termination.
a. n = Number of participants with the specified characteristic.
b. Since the participants in this row were not vaccinated, they are shown in the vaccine group to which they were randomized.
c. The values are used as the denominators for the percentage calculations.
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Demographics

Table 11: Demographic characteristics – safety population

	Vaccine Group (as Administered)								
	Sentinel Cohort 1	Sentinel Cohort 2		Sentinel Cohort 3		Sentinel Cohort 4	Sentinel-Control Cohort		Open-Label Expanded-Enrollment Stage
	Group 1 (6 Mo) MenABCWY +PLP (N^a=23) n^b (%)	Group 2 (6 Mo) MenABCWY (N^a=25) n^b (%)	Group 3 (2 Mo) 60 µg rLP2086 +Nimenrix +PLP/SLP (N^a=36) n^b (%)	Group 4 (2 Mo) 60 µg rLP2086 +Nimenrix (N^a=16) n^b (%)	Group 5 (2 Mo) 120 µg rLP2086 +Nimenrix +PLP (N^a=53) n^b (%)	Group 7 (2 Mo) MenABCWY +SLP (N^a=50) n^b (%)	Group 8 (2 Mo) Bexsero +Nimenrix +PLP (N^a=55) n^b (%)	Group 10 (2 Mo) Bexsero +Nimenrix (N^a=55) n^b (%)	Group 11 (2 Mo) MenABCWY +TLP (N^a=12) n^b (%)
Sex									
Male	11 (47.8)	15 (60.0)	15 (41.7)	9 (56.3)	29 (54.7)	23 (46.0)	23 (41.8)	35 (63.6)	5 (41.7)
Female	12 (52.2)	10 (40.0)	21 (58.3)	7 (43.8)	24 (45.3)	27 (54.0)	32 (58.2)	20 (36.4)	7 (58.3)
Race									
White	20 (87.0)	24 (96.0)	35 (97.2)	16 (100.0)	52 (98.1)	50 (100.0)	55 (100.0)	55 (100.0)	12 (100.0)
Black or African American	1 (4.3)	1 (4.0)	1 (2.8)	0	0	0	0	0	0
Asian	0	0	0	0	0	0	0	0	0
Unknown	0	0	0	0	0	0	0	0	0
Multiracial	0	0	0	0	0	0	0	0	0
Not reported	2 (8.7)	0	0	0	1 (1.9)	0	0	0	0
Ethnicity									
Hispanic or Latino	13 (56.5)	9 (36.0)	21 (58.3)	8 (50.0)	10 (18.9)	25 (50.0)	18 (32.7)	22 (40.0)	6 (50.0)
Non-Hispanic/non-Latino	10 (43.5)	16 (64.0)	15 (41.7)	8 (50.0)	43 (81.1)	25 (50.0)	37 (67.3)	33 (60.0)	6 (50.0)
Not reported	0	0	0	0	0	0	0	0	0
Age at first vaccination (days)									
Mean (SD)	158.5 (6.87)	161.6 (14.45)	71.1 (7.00)	67.6 (5.81)	68.9 (6.39)	68.0 (5.99)	67.4 (7.89)	67.5 (7.30)	69.4 (7.69)
Median	156.0	156.0	71.0	65.5	67.0	66.0	64.0	64.0	65.5
Min, max	(151, 176)	(151, 208)	(62, 88)	(61, 79)	(62, 90)	(61, 85)	(61, 97)	(61, 92)	(62, 84)

Abbreviations: Mo = months of age; PLP = prophylactic liquid paracetamol; SLP = scheduled liquid paracetamol; TLP = therapeutic liquid paracetamol.
Note: Three participants in Group 3 received 120 µg instead of 60 µg rLP2086 as result of a medication error that occurred at Vaccination 1 and were included in Group 5 for reporting.
Note: No participants were enrolled into Group 13 and Group 14 due to study termination.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
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Reactogenicity

An e-diary was used to record local reactions, systemic events, protocol-assigned paracetamol use, and other antipyretic medication use for 7 days following Vaccinations 1 and 2, and booster vaccination. Only local reactions at the site of MenABCWY, Bexsero, or bivalent rLP2086 injection (left thigh) were recorded in the e-diary.

Local reactogenicity

Primary vaccination

Tenderness at the injection site was the most commonly reported local reaction and was reported in a higher proportion of participants in the MenABCWY + SLP/TLP groups compared to the Bexsero + Nimenrix (with/without PLP) groups. (

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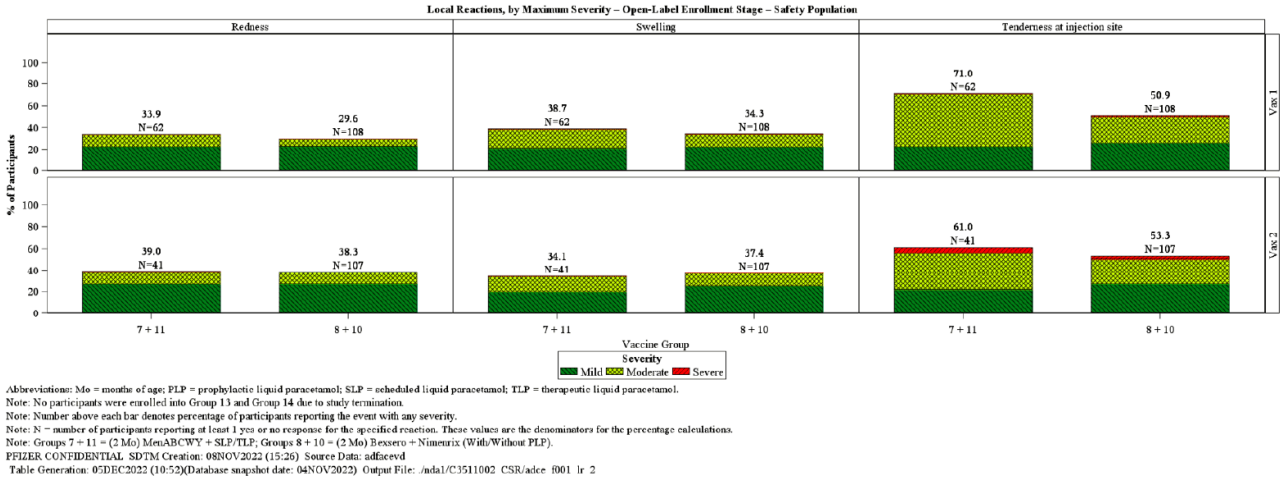

Abbreviations: Mo = months of age; PLP = prophylactic liquid paracetamol; SLP = scheduled liquid paracetamol; TLP = therapeutic liquid paracetamol.
Note: No participants were enrolled into Group 13 and Group 14 due to study termination.
Note: Number above each bar denotes percentage of participants reporting the event with any severity.
Note: N = number of participants reporting at least 1 yes or no response for the specified reaction. These values are the denominators for the percentage calculations.
Note: Groups 7 + 11 = (2 Mo) MenABCWY + SLP/TLP; Groups 8 + 10 = (2 Mo) Bexsero + Nimenrix (With/Without PLP).
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Figure 2: Local reactions, by Maximum severity, within 7 days after primary vaccinations, by vaccine groups 7 +11 and 8+10 during the Open-Label enrollment stage – safety population

In the following vaccine groups, protocol-assigned paracetamol regimens appeared to have a clinically significant impact with regard to reducing the proportion of participants with the following local reactions (**Figure *3***):

- The proportion of 6-month-old participants with any redness and any swelling within 7 days after any primary vaccination was lower in the group that received MenABCWY with PLP (Group 1) compared to the group that received MenABCWY without PLP (Group 2) (17.4% versus 48.0% for redness and 21.7% versus 56.0% for swelling).
- The proportion of 2-month-old participants with any local reaction within 7 days after Vaccination 2 was lower in the group that received Bexsero + Nimenrix with PLP (Group 8) (56.6%) compared to the group that received Bexsero + Nimenrix without PLP (Group 10) (85.2%).

There were 2 (3.2%) participants in the MenABCWY + SLP/TLP groups (Groups 7+11) and 4 (3.7%) participants in the Bexsero + Nimenrix (with/without PLP) groups (Groups 8+10) with tenderness at injection site after any vaccination that was considered severe. No local reactions led to withdrawal from the study.

The median onset for most local reactions was at the day of vaccination (Day 1.0). Most local reactions resolved within 1 to 2 days for participants in both vaccine groups with the exception of swelling which had a median duration of 2.5 days in Groups 7+11 and 4 days in Groups 8+10.

A large local reaction of redness ((>14 caliper units [>7 cm])) was reported in 1 participant 6 months of age who received MenABCWY + PLP (Group 1) after Vaccination 2 and a large local reaction of swelling was reported in 1 participant 6 months of age who received MenABCWY (Group 2) after Vaccination 1.

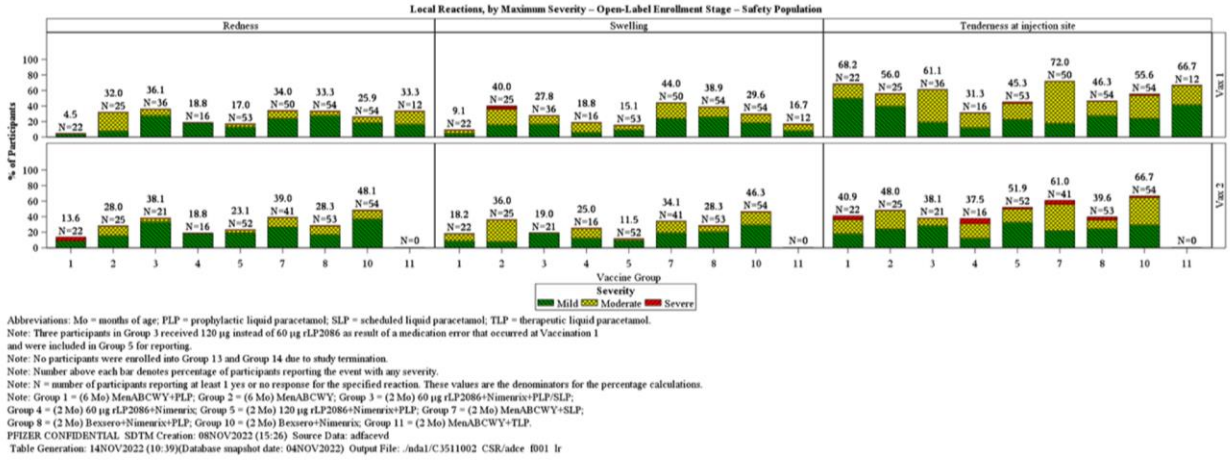


Figure 3: Local reactions by maximum severity, within 7 days after primary vaccination by vaccine group during the open label enrollment stage – safety population

Booster vaccination

In the vaccine groups that received booster vaccination (Groups 1+2, Groups 3+4, Group 5, and Groups 8+10), most local reactions after booster vaccination were mild or moderate in severity (Figure 4). Tenderness at the injection site *was the most commonly reported local reaction. The median onset for most local reactions was Day 1.0 to Day 2.0 (Day 1.0 was the day of booster vaccination) after booster vaccination for participants in Groups 1+2, Groups 3+4, Group 5, and Groups 8+10 and most local reactions resolved within 1 to 3 days.*

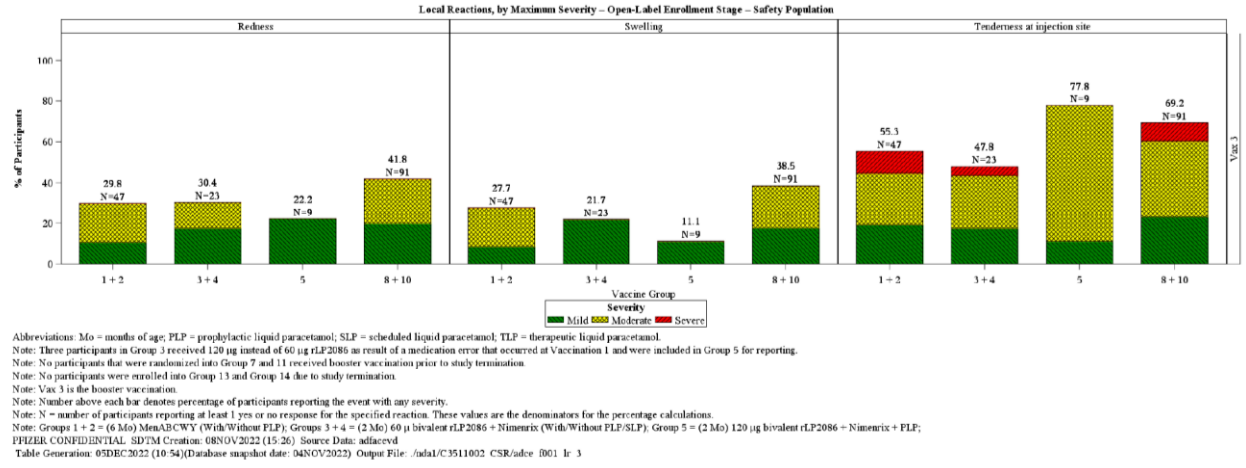
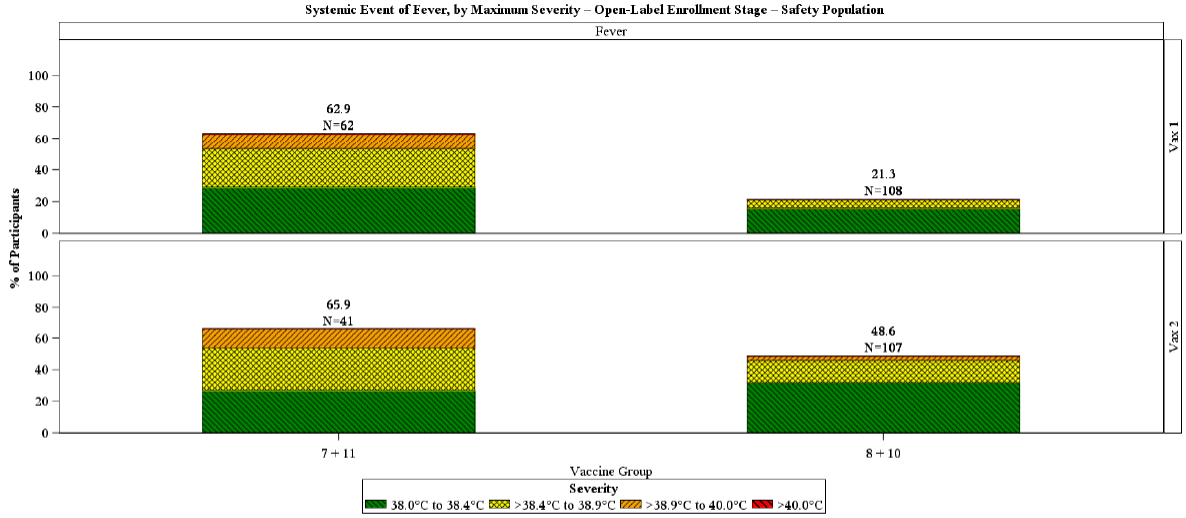


Figure 4: Local reactions by maximum severity, within 7 days after booster vaccination – safety population

Systemic reactogenicity

Primary vaccination

The proportion of participants who reported fever, decreased appetite, irritability, and drowsiness within 7 days after Vaccination 1 and Vaccination 2 was higher in participants who received MenABCWY + SLP/TLP (Groups 7+11) compared to participants who received Bexsero + Nimenrix (with/without PLP) (Groups 8+10). Irritability was the most commonly reported systemic event in Groups 7+11 and Groups 8+10 (**Figure *5***,**Error! Reference source not found.**,**Error! Reference source not found.** and **Figure *8***).



Abbreviation: Mo = months of age; PLP = prophylactic liquid paracetamol; SLP = scheduled liquid paracetamol; TLP = therapeutic liquid paracetamol.
Note: No participants were enrolled into Group 13 and Group 14 due to study termination.
Note: Number above each bar denotes percentage of participants reporting the event with any severity.
Note: N = number of participants reporting at least 1 yes or no response for the specified reaction. These values are the denominators for the percentage calculations.
Note: Group 7 + 11 = (2 Mo) MenABCWY + SLP/TLP; Group 8 + 10 = (2 Mo) Bexsero + Nimenrix (With/Without PLP).
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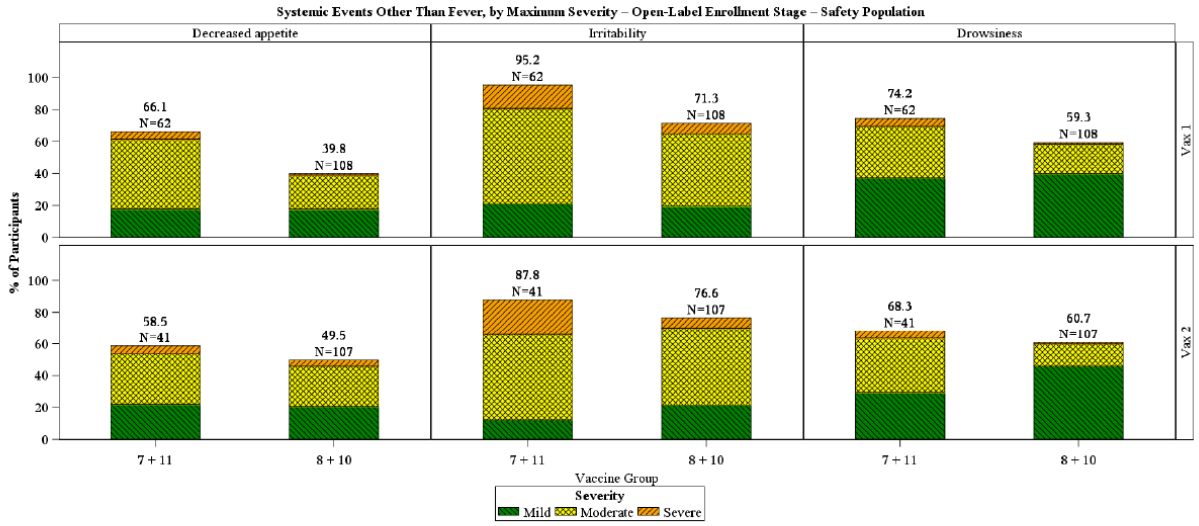
Table Generation: 30NOV2022 (12:19)
(Database snapshot date: 04NOV2022) Output File: ./nda1/C3511002 CSR/adce f001 se1 3

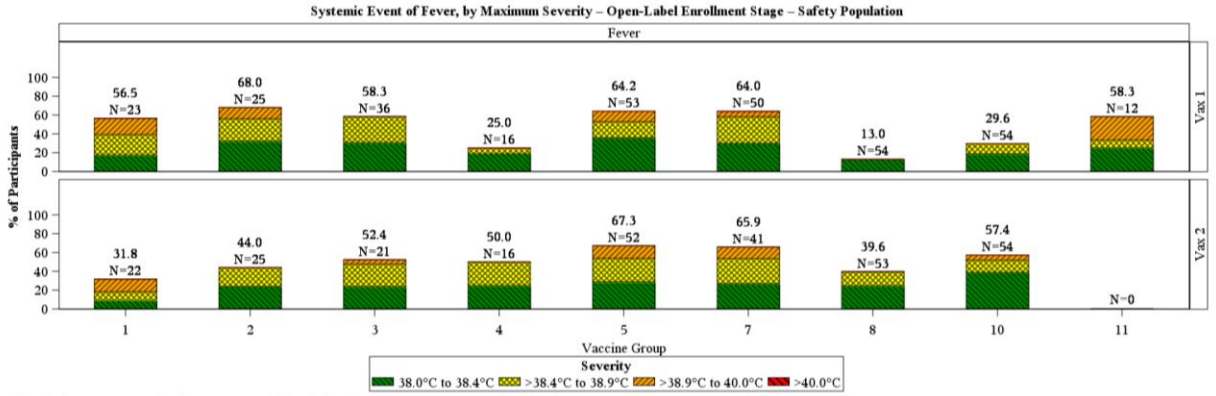
Figure 5: Systemic Event of Fever, by Maximum Severity, Within 7 Days After Primary Vaccinations, by Vaccine Groups 7+11 and 8+10 – Safety Population



Abbreviation: Mo = months of age; PLP = prophylactic liquid paracetamol; SLP = scheduled liquid paracetamol; TLP = therapeutic liquid paracetamol.
Note: No participants were enrolled into Group 13 and Group 14 due to study termination.
Note: Number above each bar denotes percentage of participants reporting the event with any severity.
Note: N = number of participants reporting at least 1 yes or no response for the specified reaction. These values are the denominators for the percentage calculations.
Note: Group 7 + 11 = (2 Mo) MenABCWY + SLP/TLP; Group 8 + 10 = (2 Mo) Bexsero + Nimenrix (With/Without PLP).
PFIZER CONFIDENTIAL SDTM Creation: 08NOV2022 (15:26) Source Data: adfacevd
Table Generation: 30NOV2022 (12:23)
(Database snapshot date: 04NOV2022) Output File: ./nda1/C3511002 CSR/adce f001 se 1

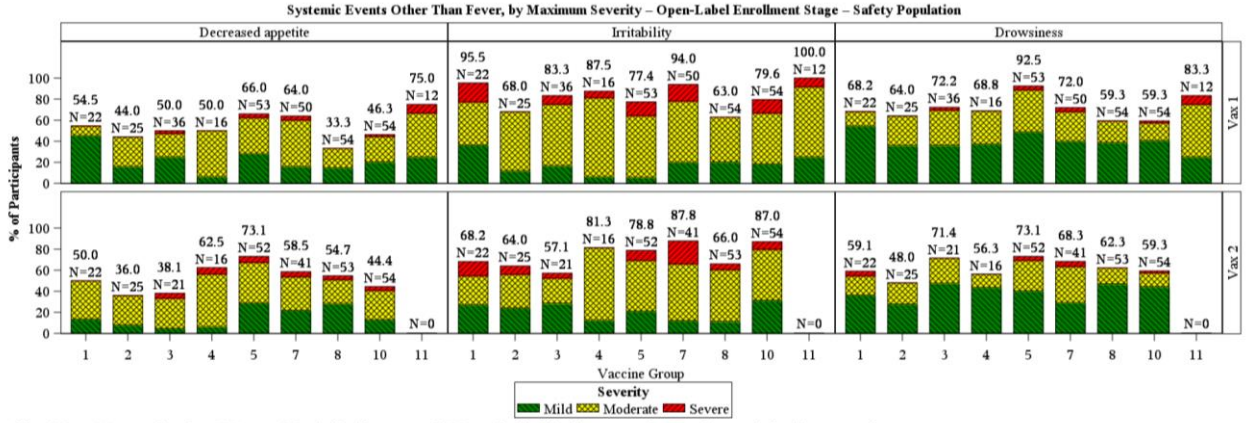
Figure 6: Systemic Events Other Than Fever, by Maximum Severity, Within 7 Days After Primary Vaccinations, by Vaccine Groups 7+11 and 8+10 – Safety Population

Overall, after the first and second primary vaccination, fever ≥38.0° C was reported in 45 of 62 participants (72.6%) in the MenABCWY + SLP/TLP groups (group 7+11) and in 61 of 109 participants (56.0%) in the Bexsero + Nimenrix (with/without PLP) groups (group 8+10) (clinical study report Supplemental Table 14.21). Of note, the 12 subjects in group 11 did not receive a second vaccination with MenABCWY. Fever >38.9° C to 40° C was reported in 10 (16.1%) participants who received MenABCWY + SLP/TLP (Groups 7+11) and in 3 (2.8%) participants who received Bexsero + Nimenrix (with/without PLP) (Groups 8+10) after any primary vaccination.



Abbreviations: Mo = months of age; PLP = prophylactic liquid paracetamol; SLP = scheduled liquid paracetamol; TLP = therapeutic liquid paracetamol.
Note: Three participants in Group 3 received 120 µg instead of 60 µg rLP2086 as result of a medication error that occurred at Vaccination 1 and were included in Group 5 for reporting.
Note: No participants were enrolled into Group 13 and Group 14 due to study termination.
Note: Number above the bar denotes percentage of participants reporting the event with any severity.
Note: N = number of participants reporting at least 1 yes or no response for the specified reaction. These values are the denominators for the percentage calculations.
Note: Group 1 = (6 Mo) MenABCWY+PLP; Group 2 = (6 Mo) MenABCWY; Group 3=(2 Mo) 60 µg rLP2086+Nimenrix+PLP/SLP; Group 4 = (2 Mo) 60 µg rLP2086+Nimenrix;
Group 5 = (2 Mo) 120 µg rLP2086+Nimenrix+PLP; Group 7 = (2 Mo) MenABCWY+SLP;
Group 8 = (2 Mo) Bexsero+Nimenrix+PLP; Group 10 = (2 Mo) Bexsero+Nimenrix; Group 11 = (2 Mo) MenABCWY+TLP.
PFIZER CONFIDENTIAL SDTM Creation: 08NOV2022 (15:26) Source Data: adfacevd
Table Generation: 14NOV2022 (10:23)
(Database snapshot date: 04NOV2022) Output File: ./nda1/C3511002 CSR/adce f001 se1

Figure 7: Systemic Event of Fever, by Maximum Severity, Within 7 Days After Primary Vaccinations – Safety Population



Abbreviations: Mo = months of age; PLP = prophylactic liquid paracetamol; SLP = scheduled liquid paracetamol; TLP = therapeutic liquid paracetamol.
Note: Three participants in Group 3 received 120 µg instead of 60 µg rLP2086 as result of a medication error that occurred at Vaccination 1 and were included in Group 5 for reporting.
Note: No participants were enrolled into Group 13 and Group 14 due to study termination.
Note: Number above each bar denotes percentage of participants reporting the event with any severity.
Note: N = number of participants reporting at least 1 yes or no response for the specified reaction. These values are the denominators for the percentage calculations.
Note: Group 1 = (6 Mo) MenABCWY+PLP; Group 2 = (6 Mo) MenABCWY; Group 3 = (2 Mo) 60 µg rLP2086+Nimenrix+PLP/SLP; Group 4 = (2 Mo) 60 µg rLP2086+Nimenrix;
Group 5 = (2 Mo) 120 µg rLP2086+Nimenrix+PLP; Group 7 = (2 Mo) MenABCWY+SLP;
Group 8 = (2 Mo) Bexsero+Nimenrix+PLP; Group 10 = (2 Mo) Bexsero+Nimenrix; Group 11 = (2 Mo) MenABCWY+TLP.
PFIZER CONFIDENTIAL SDTM Creation: 08NOV2022 (15:26) Source Data: adfacevd
Table Generation: 14NOV2022 (12:33)
(Database snapshot date: 04NOV2022) Output File: ./nda1/C3511002 CSR/adce f001 se

Figure 8: Systemic Events Other Than Fever, by Maximum Severity, Within 7 Days After Primary Vaccinations – Safety Population

Assessors comment:

The Frequency of fever is significantly higher for all groups where MenABCWY or bivalent rLP2086 + Nimenrix have been administered compared to Bexsero + Nimenrix, ranging from 25% until 68% where 6 out of 7 groups have a frequency above 56 % (Figure 4). Frequency of fever for Bexsero + Nimenrix overall ranged from 13% to 57.4%. It is unclear why group 4 with n=16 has a lower frequency of fever compared to group 3 (60 µg bivalent rLP2086 + Nimenrix + PLP/SLP) despite not being on a controlled paracetamol scheme. The frequency of fever was higher after the second dose except for group 1, 2 and 3.

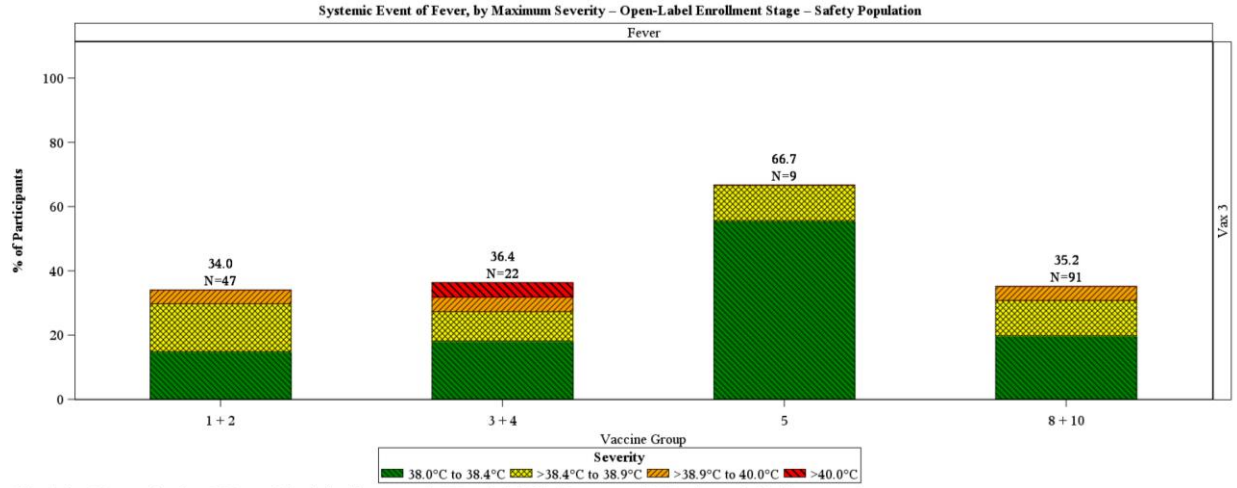
Booster vaccination

As a result of study termination, participants in Group 7 and Group 11 did not receive a booster vaccination with MenABCWY. In the vaccine groups that received booster vaccination (Groups 1+2, Groups 3+4, Group 5, and Groups 8+10), most systemic events within 7 days after booster vaccination were mild or moderate in severity (

and

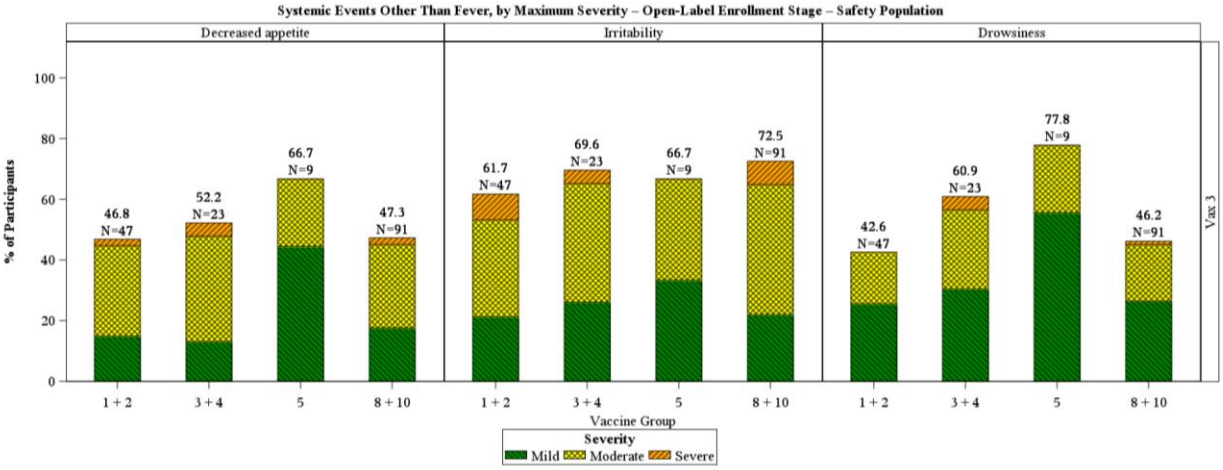
). Drowsiness and irritability were the most commonly reported systemic events.

The median onset for most systemic events was Day 1.0 to Day 2.0 (Day 1.0 was the day of booster vaccination) after booster vaccination for participants in Groups 1+2, Groups 3+4, Group 5, and Groups 8+10 and most systemic events resolved within 1 to 3 days.



Abbreviation: Mo = months of age; PLP = prophylactic liquid paracetamol; SLP = scheduled liquid paracetamol; TLP = therapeutic liquid paracetamol.
Note: Three participants in Group 3 received 120 µg instead of 60 µg rLP2086 as result of a medication error that occurred at Vaccination 1 and were included in Group 5 for reporting.
Note: No participants that were randomized into Group 7 and 11 received booster vaccination prior to study termination.
Note: No participants were enrolled into Group 13 and Group 14 due to study termination.
Note: Vax 3 is the booster vaccination.
Note: Number above each bar denotes percentage of participants reporting the event with any severity.
Note: N = number of participants reporting at least 1 yes or no response for the specified reaction. These values are the denominators for the percentage calculations.
Note: Groups 1 + 2 = (6 Mo) MenABCWY (With/Without PLP); Groups 3 + 4 = (2 Mo) 60 µ bivalent rLP2086 + Nimenrix recipients (With/Without PLP/SLP);
PFIZER CONFIDENTIAL SDTM Creation: 08NOV2022 (15:26) Source Data: adfacevd
Table Generation: 05DEC2022 (10:58)
(Database snapshot date: 04NOV2022) Output File: ./nda1/C3511002 CSR/adce f001 se1 2

Figure 9: Systemic Event of Fever, by Maximum Severity, Within 7 Days After Booster Vaccination – Safety Population



Abbreviations: Mo = months of age; PLP = prophylactic liquid paracetamol; SLP = scheduled liquid paracetamol; TLP = therapeutic liquid paracetamol.
Note: Three participants in Group 3 received 120 µg instead of 60 µg rLP2086 as result of a medication error that occurred at Vaccination 1 and were included in Group 5 for reporting.
Note: No participants that were randomized into Group 7 and 11 received booster vaccination prior to study termination.
Note: No participants were enrolled into Group 13 and Group 14 due to study termination.
Note: Vax 3 is the booster vaccination.
Note: Number above each bar denotes percentage of participants reporting the event with any severity.
Note: N = number of participants reporting at least 1 yes or no response for the specified reaction. These values are the denominators for the percentage calculations.
Note: Groups 1 + 2 = (6 Mo) MenABCWY (With/Without PLP); Groups 3 + 4 = (2 Mo) 60 µ bivalent rLP2086 + Nimenrix (With/Without PLP/SLP); Group 5 = (2 Mo) 120 µg bivalent rLP2086 + Nimenrix + PLP; Groups 7 + 11 = (2 Mo) MenABCWY + SLP/TLP; Groups 8 + 10 = (2 Mo) Bexsero + Nimenrix (With/Without PLP).
PFIZER CONFIDENTIAL SDTM Creation: 08NOV2022 (15:26) Source Data: adfacevd
Table Generation: 30NOV2022 (12:25)
(Database snapshot date: 04NOV2022) Output File: ./nda1/C3511002 CSR/adce f001 se 2

Figure 10: Systemic Events Other Than Fever, by Maximum Severity, Within 7 Days After Booster Vaccination – Safety Population

Adverse events overall

Primary vaccination

The most commonly reported SOC was Infections and infestations, reported in 30 (48.4%) participants who received MenABCWY + SLP/TLP (Groups 7+11) and 23 (20.9%) participants who received Bexsero + Nimenrix (with/without PLP) (Groups 8+10), none of which were considered related to vaccine.

The proportion of participants with AEs in the SOCs of Metabolism and nutrition disorders, Musculoskeletal and connective tissue disorders, Nervous system disorders, and Psychiatric disorders was generally higher in the MenABCWY + SLP/TLP groups relative to the Bexsero + Nimenrix (with/without PLP) groups.

During the primary series vaccination phase, there was an imbalance in the proportion of participants who reported at least 1 AE, which was higher in the MenABCWY + SLP/TLP groups (Groups 7+11; 56.5%) compared to the Bexsero + Nimenrix (with/without PLP) groups (Groups 8+10; 33.6%). A similar trend was observed with regard to the proportion of participants who reported related AEs, severe AEs, SAEs, and MAEs.

The majority of related AEs were in SOCs that correspond to reactogenicity-type events (General disorders and administration site conditions, Metabolism and nutrition disorders, Musculoskeletal and connective tissue disorders, Nervous system disorders, and Psychiatric disorders), with the most common PTs including decreased appetite, pain in extremity, somnolence, and irritability. For MenABCWY + SLP/TLP groups (7+11) 14.5% of the AEs reported 30 days after any primary vaccination were evaluated to be related compared to 4.5% for Bexsero + Nimenrix (with/without PLP) groups (8+10).

Overall, 7 severe AEs were reported in a total of 6 participants during the primary vaccination phase. Severe AEs that were considered related to vaccine were reactogenicity-type events (two reports of irritability and one report of pyrexia). No severe AEs were reported during the primary follow-up phase.

Booster vaccination

The most commonly reported SOC was Infections and infestations across the groups that received booster vaccination with MenABCWY (with/without PLP) (6-month-old participants [Group 1 and Group 2]), bivalent rLP2086 (60 µg or 120 µg) + Nimenrix (with/without PLP/SLP) (Groups 3 through 5), and Bexsero + Nimenrix (with/without PLP) (Groups 8+10). One of the MAEs (pyrexia) was considered related in one participant who received MenABCWY + PLP (Group 1) and there were no newly diagnosed chronic medical conditions (NDCMCs) reported during the booster vaccination phase.

One participant who received a booster vaccination of 120 µg bivalent rLP2086 + Nimenrix (Group 5) reported Bacillus cereus bacteremic gastroenteritis, which was categorised as a severe AE and an SAE but was not considered related to study intervention or clinical trial procedures. Across the groups that received booster vaccination, related AEs were reactogenicity events (pyrexia and irritability).

There were no related or severe AEs and no NDCMCs were reported during the booster follow-up phase. The most commonly reported SOC was Infections and infestations.

Deaths

There was one death reported during the study in a non-Hispanic/non-Latino male participant who received MenABCWY + SLP (Group 7) and was 2 months old at the time of enrolment. The participant died from sudden infant death syndrome (SIDS) 22 days after receiving Vaccination 2. An autopsy determined the cause of death as SIDS in the context of a cardiac anomaly, described in the autopsy report as an "anomaly of the origin of the right coronary artery." The investigator considered that there was not a reasonable possibility that the SIDS was related to study intervention or clinical trial procedures.

Medically attended adverse events (MAEs)

The most commonly reported SOC for MAEs was Infections and infestations, which represents events (PTs) expected in this age group such as conjunctivitis, gastroenteritis, nasopharyngitis, otitis media acute, and upper respiratory tract infection. The proportion of participants who reported MAEs in the SOC of Infections and infestations was generally higher in participants enrolled at 6 months of age who received MenABCWY (with or without PLP; Group 1 and Group 2) compared to participants enrolled at 2 months of age in Group 3, Group 5, Group 7, Group 8, and Group 10. There were 6 related MAEs reported in 4 participants, some of which were reactogenicity events (3 reports of pyrexia and 1 report of irritability) and 2 that were reports of vomiting that were accompanied by systemic events of pyrexia and irritability.

Serious Adverse events

The most commonly reported SOC was Infections and infestations and none of the SAEs were considered related to vaccine. There was a higher number (20.8%) of SAEs reported in participants who received 120 µg bivalent rLP2086 + Nimenrix + PLP (Group 5) relative to participants in other vaccine groups (0% to 10.9%) (**Table *12***).

Table 12: Serious Adverse events reported during the study – safety population

	Vaccine Group (as Administered)								
	Sentinel Cohort 1	Sentinel Cohort 2		Sentinel Cohort 3		Sentinel Cohort 4	Sentinel-Control Cohort		Open-Label Expanded-Enrollment Stage
	Group 1 (6 Mo) MenABCWY +PLP (N^a=23)	Group 2 (6 Mo) MenABCWY (N^a=25)	Group 3 (2 Mo) 60 µg rLP2086 +Nimenrix +PLP/SLP (N^a=36)	Group 4 (2 Mo) 60 µg rLP2086 +Nimenrix (N^a=16)	Group 5 (2 Mo) 120 µg rLP2086 +Nimenrix +PLP (N^a=53)	Group 7 (2 Mo) MenABCWY +SLP (N^a=50)	Group 8 (2 Mo) Bexsero +Nimenrix +PLP (N^a=55)	Group 10 (2 Mo) Bexsero +Nimenrix (N^a=55)	Group 11 (2 Mo) MenABCWY +TLP (N^a=12)
System Organ Class Preferred Term	n^b (%) (95% CI^c) No. of Events^d	n^b (%) (95% CI^c) No. of Events^d	n^b (%) (95% CI^c) No. of Events^d	n^b (%) (95% CI^c) No. of Events^d	n^b (%) (95% CI^c) No. of Events^d	n^b (%) (95% CI^c) No. of Events^d	n^b (%) (95% CI^c) No. of Events^d	n^b (%) (95% CI^c) No. of Events^d	n^b (%) (95% CI^c) No. of Events^d
Any event	0 (0.0, 14.8)	1 (4.0) (0.1, 20.4)	1 (2.8) (0.1, 14.5)	1 (6.3) (0.2, 30.2)	11 (20.8) (10.8, 34.1)	5 (10.0) (3.3, 21.8)	1 (1.8) (0.0, 9.7)	6 (10.9) (4.1, 22.2)	1 (8.3) (0.2, 38.5)

None of the SAEs were ultimately considered by the investigator to be related to vaccine. The following SAEs met the criteria of a protocol-defined stopping rule:

- A non-Hispanic/non-Latino male participant who received MenABCWY + SLP (Group 7) and was 2 months old at the time of enrollment died from SIDS 22 days after receiving Vaccination 2 administered at 4 months of age. This was classified as an SAE and the investigator considered

that there was not a reasonable possibility that the SIDS was related to study intervention or clinical trial procedure.

- A White Hispanic/Latino female participant who was 2 months old at the time of enrollment into the 120 µg bivalent rLP2086 + Nimenrix + PLP group (Group 5) and 12 months old at the time of booster vaccination developed a fever 1 day after receiving a booster vaccination of 120 µg bivalent rLP2086 + Nimenrix. The fever initially subsided with antipyretics, but the participant started having persistent fever that did not respond to antipyretics, a positive blood culture for Bacillus cereus was reported which led to a diagnosis of Bacillus cereus bacteremic gastroenteritis. The investigator considered that there was not a reasonable possibility that the Bacillus cereus bacteremic gastroenteritis was related to study intervention or clinical trial procedures. The participant was withdrawn from further study interventions because of study termination by the sponsor and was followed up for safety.
- A 2-month-old participant developed fever and was admitted to the hospital within 2 days of receiving the first vaccination of 120 µg bivalent rLP2086 + Nimenrix with prophylactic paracetamol. A lumbar puncture was performed which revealed 18 white blood cells (WBCs). Cerebrospinal fluid (CSF), blood cultures, and investigations for pathogens at the admitting hospital were negative and symptoms resolved. A molecular analysis from the certified laboratory of the coordinating investigator later revealed Human Herpes Virus 7 in the blood.
- A 2-month-old infant was admitted to the hospital within 2 days after receiving the first dose of MenABCWY and presented with fever, irritability, vomiting, and reluctancy to eat. A workup was done which included a lumbar puncture that revealed 720 leukocytes in the CSF. CSF, blood cultures, and investigations for pathogens were negative.
- Following the reporting of the last case of CSF pleocytosis in Study C3511002, Pfizer performed a review of all extant safety data, including another SAE (similar in nature to the 2 SAEs reported in Study C3511002) in a 2-month-old infant who received 60 µg bivalent rLP2086, which was previously reported in Study B1971008 (NCT00798304).).

Assessors comment:

The MAH provided limited information in the clinical study report and clinical overview regarding a similar case reported in the phase 1/2 study B1971008 (NCT00798304) after vaccination with Trumenba. The assessors have found more information in the published article by Martinon-Torres et al. 2014 describing the study.

The case concerns a SAE of aseptic meningitis approximately 10 hours after vaccination with rLP2086 together with Prevenar, Infanrix hexa, Meningitec and Rotarix. The subject developed fever (39.0 degrees) and spinal puncture found 500 cells (95% polymorphonuclear leukocyte – PMNs). Bacterial and viral cultures were negative. Although the aseptic meningitis was ultimately considered not vaccine related by the treating physician, review of safety data by a project-independent safety committee revealed that 90% of vaccine recipients at the 60 µg dose level experienced mild to moderate fever. (Martinon-Torres et al. 2014 "A randomized, phase 1/2 trial of the safety, tolerability, and immunogenicity of bivalent rLP2086 meningococcal B vaccine in healthy infants", Vaccine volume 32 issue 40 https://www.sciencedirect.com/science/article/pii/S0264410X1400992X?via%3Dihub).

This case led to a safety review. Based on this safety review, the sponsor decided to terminate the study early.

Safety-Related Participant Withdrawals

There were 2 participants who were withdrawn from the study due to non-serious adverse events and in both cases, the caregiver withdrew consent.

2.3.3. Discussion on clinical aspects

Immunogenicity:

There are no treatment arms on Nimenrix administered without MenB in this study. Although Nimenrix is included in all study arms, either as part of MenABCWY or co-administered with rLP2086, immunogenicity data has only been provided for groups 7, 8 and 10 which included children aged 2 months. This is partly due to a) early termination of the study, b) following protocol amendment which removed certain arms from the study (Group 6 and Group 9) and c) lack of available sera (Groups 1 and 2) since this was prioritised for assay development.

Primary vaccination involved two administrations 2 months apart (Month 0 and month 2). Booster immunisation occurred at month 12 (10 months after primary immunisation) for groups 8 and 10 but were not administered to group 7 due to trial termination.

The primary endpoint assessed data from Groups 7, 8 and 10. Concomitant paracetamol for vaccination with Nimenrix/Bexsero (groups 8 and 10) did not affect the number of individuals achieving a titre of $\geq$1:8 (defined as the LLOQ) following primary vaccination. When comparing to data from the Nimenrix SmPC in children aged 6-12 weeks (compared to 2 months/8 weeks in this study), the proportion of participants attaining titres fulfilling the LLOQ for hSBA towards each antigen was similar (96.5%-100%). The number of participants in the SmPC was larger (over 450 participants per arm) compared to n=16 (Group 7), n=43 (Group 8) and n=47 (Group 10).

GMT following primary vaccination between group 7 and groups 8 and 10 were similar although slightly higher towards MenY for groups 8 and 10 [GMT: 921.5 (95% CI:825.1, 1029.11)] compared to group 7 [GMT: 583.1 (95% CI: 416.5, 816.2)]. Conversely, responses to MenW were higher in the MenABCWY (Group7) (GMT:317.9 (95% CI: 218.6, 462.4)] compared to groups 7 and 8 (GMT:124.2 (95% CI: 105.3,146.5)]. Responses to MenA and MenC were comparable between group 7 and groups 8 + 10 combined.

After booster immunisation, which was given to groups 8 and 10, responses were greatest to MenY [GMT: 3343.9 (95% CI: 2683.2, 4167.2)] and lowest to MenC, and it was clear that an anamnestic response was induced.

Overall, the GMT were lower than those described in Table 2 of the SmPC (see Annex 1) for the similar age group. It is not known if co-administration of MenB (Trumenba) in Group 7, and Bexsero in Groups 8 and 10), may have affected responses to MenA,C,W and Y in this study. The titres shown in the Nimenrix SmPC (Table 2 – Annex 1), participants had also received DTaP-HBV-IPV/Hib and a 10-valent pneumococcal vaccine. However, this was also a feature of this study, where participants received the same, DTaP-HBV-IPV/Hib and a 13-valent pneumococcal vaccine. This could suggest that responses to MenB may have affected immune responses to menACWY.

According to the SmPC, Nimenrix may be given concomitantly with a number of different vaccines such as hepatitis A (HAV), hepatitis B (HBV) and measles mumps rubella (MMR) in addition to DTaP-HBV-IPV/Hib and a 10-valent pneumococcal vaccine. However, there is currently no mention of concomitant administration with a MenB vaccine such as Bexsero.

Currently the data provided are too limited to support inclusion of Bexsero as a vaccine that can be given concomitantly with Nimenrix. Furthermore, concomitant administration of Nimenrix and Trumenba to children aged 2 months as described in the clinical study C3511002 is outside the current

indication of Trumenba (≥10 years of age). Therefore, the immunogenicity data presented for the clinical study C3511002 is currently insufficient to warrant any changes to the SmPC for Nimenrix.

Safety:

Nimenrix was administered either concomitantly with Trumenba as part of MenABCWY (Group 1, 2, 7 and 11) and in the groups receiving rLP2086 (Trumenba) + Nimenrix (Group 3, 4, 5) or with Bexsero (Group 8 and 10). In addition, subjects in all groups were vaccinated with Vaxelis (DTaP-HBV-IPV/Hib) and Prevenar 13 (13-valent pneumococcal polysaccharide conjugate vaccine) concomitantly with the study vaccines (group 1-2: 1st vaccination and group 3-11: 1st and 2nd vaccination).

Local reactogenicity was not recorded for Nimenrix as per protocol for study C3511002, thus for the groups 3-5 and 8+10 only local reactogenic AEs after rLP2086 and Bexsero administration, respectively, were included in the safety analysis. Fever occurred more frequently after rLP2086 + Nimenrix administration than after Nimenrix + Bexsero administration independently of the paracetamol regimen. Only subjects receiving the lower dose of rLP2086 (60 µg) in combination with Nimenrix showed a lower or similar frequency of fever.

One death due to SIDS was reported in a 2-month-old subject 22 days after receiving Vaccination 2 with MenABCWY + SLP (Group 7). The investigator considered that the case of SIDS was not related to study vaccination.

A case of aseptic meningitis including CSF pleocytosis was reported in an earlier study (B1971008) in a 2-month-old infant after administration of 60 µg rLP2086. This case triggered a safety review and subsequently resulted in the early termination of this study.

In the current study, two serious cases of CSF pleocytosis were reported in infants 2 months of age who were admitted to the hospital with persistent fever shortly after vaccinations with 120 µg rLP2086 + Nimenrix or MenABCWY, and where evaluations revealed CSF pleocytosis. These cases triggered a safety review which included a statistical analysis using the background rate of aseptic meningitis in Europe. The review showed that it was extremely unlikely that a total of three cases of CSF pleocytosis occurred by chance shortly after vaccination and the study was terminated as a result.

Nimenrix has had MA in EU since 2012, and approximately 40 166 039 units were distributed cumulatively worldwide with an estimated exposure of 36 832 258 subjects in the age group 0-16 years (until 19 April 2022, Periodic Safety Update Report nr 15). Only one case of CSF pleocytosis and four cases of aseptic meningitis were retrieved from VigiBase for Nimenrix. Trumenba is indicated for individuals 10 years and older and is known to be more reactogenic than Nimenrix causing high rates of fever in infants and young children. In addition, the SmPC for the MenB vaccine Bexsero lists meningeal irritation as an ADR in children up to 10 years of age.

Based on the limited data from the current study and the earlier terminated study (B1971008), the safety profile of the combination vaccines containing Nimenrix and Trumenba does not seem acceptable in 2- to 6-month-old children. Considering the well-known safety profile of Nimenrix in infants and the high reactogenicity of Trumenba in younger children, it cannot be ruled out that the high reactogenicity of the combination vaccines is related to the Trumenba component.

The data provided from study C3511002 represent Nimenrix given in combination with other menB-vaccine. For Trumenba the age cohorts were off label.

The provided safety data does not raise any new safety concerns clearly related to Nimenrix alone. Furthermore, the data is insufficient to support the inclusion of safety information from this study in the SmPC as a) Nimenrix was only administered concomitantly with MenB vaccines (Trumenba and Bexsero), b) local reactogenicity for Nimenrix was not recorded and c) the study was terminated early.

3. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

The MAH should provide a written explanation as to why safety data from Groups 1 and 2 involving only the pentavalent meningococcal vaccine (MenABCWY) were submitted as part of this procedure but not the immunogenicity data.

The timetable is a 30-day response timetable without clock stop.

MAH responses to Request for supplementary information

Pfizer would like to highlight that all available safety and immunogenicity data from the groups who received Nimenrix have already been reported in the Clinical Study Report (CSR) as per the protocol-defined objectives, estimands, and endpoints described in Protocol Section 3. Participants enrolled into Group 1 (6-month-olds, MenABCWY with Prophylactic Liquid Paracetamol [PLP]) and Group 2 (6-month-olds, MenABCWY without PLP) did not receive Nimenrix. No further immunogenicity data will be provided in the future due to sera volume limitations and assay development work (see below).

Protocol objectives pertinent to Groups 1 and 2, both safety and immunogenicity, were categorized as tertiary/exploratory in nature:

- Safety data from Groups 1 and 2 were an integral part of the sentinel design of the study as described in Protocol Section 4.1. Safety data from these groups were essential to inform decision making in relation to study progression to younger age groups as described in Protocol Section 4.1.1.1. The safety data from these groups were collected and therefore reported as per protocol.

- Protocol Section 3 outlines that sera obtained from participants enrolled in the open-label stages may be used for exploratory analysis and meningococcal assay development as a priority over the analysis of estimands based on availability of serum volume. Following this protocol provision, sera obtained from participants in Groups 1 and 2 were used as a priority for exploratory testing in support of assay development. As a result, due to remaining serum volume limitations, it was not possible to complete a meaningful analysis in support of the immunogenicity objectives for all 5 serogroups pertinent to Group 1 and 2 who received MenABCWY (as described in Protocol Section 3). The CSR states that these may be reported in a future supplemental report. However, this statement was contingent upon serum volume availability and because of this limitation, no further immunogenicity data will be provided in the future as part of a supplemental report to the CSR.

Assessor's comment:

Nimenrix is a constituent of MenABCWY where Nimenrix (MenACWY) and MenB (Trumenba) were administered within the same injection whilst the control groups involved administration of Nimenrix and MenB (Bexsero) as separate injections. No study group included Nimenrix alone.

The provision described by the MAH whereby sera from the open label stages of the study may be used for assay development was introduced as part of Amendment 1 of the protocol. It is acknowledged that

in the absence of available sera, it will not be possible to carry out any immunogenicity analyses for groups 1 and 2.

The response received is considered acceptable.

4. Rapporteur's overall conclusion and recommendation

The immunogenicity data provided are limited and do not currently support any changes to the SmPC. Of note, there were no treatment arms with Nimenrix alone in the submitted study. Furthermore, there is insufficient data to assess whether inclusion of Bexsero for concomitant immunisation with Nimenrix can be included in the SmPC section 4.5.

No new safety concerns or adverse reactions for Nimenrix were identified in this study, and no changes to the SmPC are warranted. The presented safety data is insufficient to support the inclusion of safety information from this study in the SmPC.

☒ Fulfilled:

No regulatory action required.