12 October 2023
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Human Medicines Division

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

Trumenba

Meningococcal group B vaccine (recombinant, adsorbed)

Procedure no: EMEA/H/C/004051/P46/017

Note

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

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	27 Mar 2023	27 Mar 2023
☐	CHMP Rapporteur Assessment Report	02 May 2023	03 May 2023
☐	CHMP members comments	15 May 2023	n/a
☐	Updated CHMP Rapporteur Assessment Report	17 May 2023	n/a
☐	request for supplementary information	25 May 2023	25 May 2023
☐	Submission	12 Sep 2023	24 Aug 2023
☐	Re-start	13 Sep 2023	13 Sep 2023
☐	CHMP Rapporteur Assessment Report	27 Sep 2023	27 Sep 2023
☐	CHMP members comments	02 Oct 2023	n/a
☐	Updated CHMP Rapporteur Assessment Report	05 Oct 2023	n/a
☒	CHMP adoption of conclusions:	12 Oct 2023	12 Oct 2023

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1. Introduction

On 14 March 2023, the MAH submitted a completed paediatric study for Trumenba, 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 C3511002 "a phase 2b trial to assess the safety, tolerability, and immunogenicity of MenABCWY in healthy infants 2 and 6 months of age", is a stand-alone study.

The study investigated the pentavalent meningococcal vaccine MenABCWY (composed of Trumenba and Nimenrix mixed to administer in a single injection). Comparisons were made to co-administration of Trumenba (full dose or half dose; 120 or 60 µg) and Nimenrix, and co-administration of Bexsero and Nimenrix. Considering this is an article 46 procedure within the Trumenba dossier, this assessment will only focus on the groups in which Trumenba, both full and half dose, was co-administered with Nimenrix.

The study was terminated early due 2 cases of fever requiring clinical and laboratory investigations in infants 2 months of age which met the protocol-defined criteria for a stopping rule. As a result of study termination, the majority of participants did not complete the study.

2.2. Information on the pharmaceutical formulation used in the study

The manufacturing lot numbers for the study interventions dispensed in this study are provided in Table 1.

Table 1. Investigational Product Lot Numbers – Final

Investigational Product	**Manufacturer**	**Vendor Lot Number (Manufacturer)**	**Lot Number[a] (Pfizer)**
Bivalent rLP2086[b]	Pfizer	CL3237	20-000165
Trumenba[b]	Pfizer	DA4348	19-005010
Nimenrix (MenACWY-TT)[b]	Pfizer	DK9946 DP9710	20-000490 20-002294
Prevenar 13	Pfizer	DN4736	20-001730
Bexsero	GSK Vaccine S.r.l.	ABXA69CC ABXB61AB	20-002512 21-AE-00119
Vaxelis	MCM Vaccine B.V.	S033585	20-002001
Paracetamol	Farmaclair	V716 X703	20-002347 21-AE-00214
a. Lot number assigned to the investigational product by Pfizer Global Clinical Supply. b. Bivalent rLP2086 solution and Trumenba solution were used to reconstitute Nimenrix lyophilized powder to formulate MenABCWY.			

The planned dosing schedule for each study intervention is summarised in Table 2.

Table 2. Planned Study Intervention Administration Schedule

Investigational Product	Group(s)	Visit(s)	Injection Location
MenABCWY	1, 2, 7, 11, and 13	Visits 1, 3, and 5	Left thigh
Trumenba (60-µg dose)	3 and 4	Visits 1, 3, and 5	Left thigh
Trumenba 120-µg dose)	5	Visits 1, 3, and 5	Left thigh
Nimenrix	3, 4, 5, 8, 10, and 14	Visits 1, 3, and 5	Right thigh
Bexsero	8, 10, and 14	Visits 1, 3, and 5	Left thigh
Placebo	13	Visits 1, 3, and 5	Right thigh
Prevenar 13	1 and 2	Visit 1	Right thigh
	3-5, 7, 8, 10, 11, 13, and 14	Visits 1 and 3	Right thigh
Vaxelis	1 and 2	Visit 1	Right thigh
	3-5, 7, 8, 10, 11, 13, and 14	Visits 1 and 3	Right thigh
Paracetamol[a]	1, 3, 5, 7, 8, 11, 13, and 14	Visits 1 and 3	Not applicable
As a result of study termination on 17 March 2022, the study did not complete as originally intended and all study vaccinations and blood draws were stopped in response to this decision. Consequently, the majority of participants did not complete the study. a. Liquid paracetamol 120 mg or 60 mg was provided prophylactically, via a schedule or therapeutically.			

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study C3511002: "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 termination

The study was terminated as 2 cases of fever requiring invasive investigations were reported in infants 2 months of age and both met protocol-defined criteria for a stopping rule.

As a result of study termination, the majority of participants did not complete the study, as detailed below.

For groups enrolling participants 2 months of age:

- Group 3 (60 µg bivalent rLP2086 + Nimenrix + Prophylactic Liquid Paracetamol (PLP)/ Scheduled Liquid Paracetamol (SLP)): enrollment was completed but only a proportion of those enrolled completed the primary series, and only a proportion of those completing the primary series progressed to a booster dose.
- Group 4 (60 µg bivalent rLP2086 + Nimenrix): enrollment not completed (17 participants were randomised, out of the 25 planned) based on a recommendation from the Independent Review Committee (IRC) and Data Monitoring Committee (DMC) that no further participants could be enrolled into Group 4 which did not contain any protocol-assigned paracetamol regimen as part of the study intervention. Primary series vaccinations were completed but only a proportion of those completing the primary series progressed to a booster dose. Post-booster blood draws were not performed, and post-booster immunogenicity data were not reported.

- Group 5 (120 µg bivalent rLP2086 + Nimenrix + PLP): enrollment and primary series vaccinations were completed but only a proportion of those completing the primary series progressed to a booster dose. Post-booster blood draws were not performed, and post-booster immunogenicity data were not reported. There were 2 Serious Adverse Events (SAEs) in this group that met the criteria for a protocol-defined stopping rule.
- Group 7 (MenABCWY + SLP): enrollment was completed but only a proportion of those enrolled completed the primary series vaccinations. None of the participants received a booster vaccination of MenABCWY. There was one event in this group that met the criteria for a protocol-defined stopping rule.
- Group 11 (MenABCWY + TLP): enrollment into the open-label expanded-enrollment stage was not completed (only 12 participants were randomised out of 50-100 that were planned to be enrolled) and none of the participants already enrolled in Group 11 received Vaccination 2 of the primary vaccination series or the MenABCWY booster vaccination. There was one event in this group that met the criteria for a protocol-defined stopping rule.
- Group 8 (Bexsero + Nimenrix + PLP): enrollment and primary series vaccination were completed but only a proportion of those completing the primary series progressed to a booster dose.
- Group 10 (Bexsero + Nimenrix without PLP): enrollment and primary series vaccination were completed but only a proportion of those completing the primary series progressed to a booster dose.
- 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 Therapeutic Liquid Paracetamol (TLP)).

The groups that enrolled participants 6 months of age who received MenABCWY (Group 1 and Group 2) were not impacted by study termination and completed enrollment and all study interventions.

Assessor's comment

As the study was terminated early, the information that can be obtained regarding Trumenba is limited. Information on immunogenicity of Trumenba can be obtained from Groups 3, 4 and 5, in which Trumenba, either 60 µg or 120 µg, was administered concomitantly with Nimenrix. Information for safety might be obtained from some of the other groups as well, as Trumenba was part of the newly developed pentavalent MenABCWY vaccination.

Due to study termination, the information that can be obtained is limited, as the majority of participants in these groups did not complete the regimen of a primary vaccination of 2 doses and a booster dose following at least 6 months after the primary vaccination. In addition, for Group 4 and 5 no post-booster blood draws were taken and therefore no information on immunogenicity was provided.

Methods

This was a Phase IIb, multi-centre study with 3 stages: an open-label sentinel-cohort stage, an open-label expanded-enrollment stage, and a blinded expanded-enrollment stage. An overview of the planned study progression through these stages is shown in Figure 1.

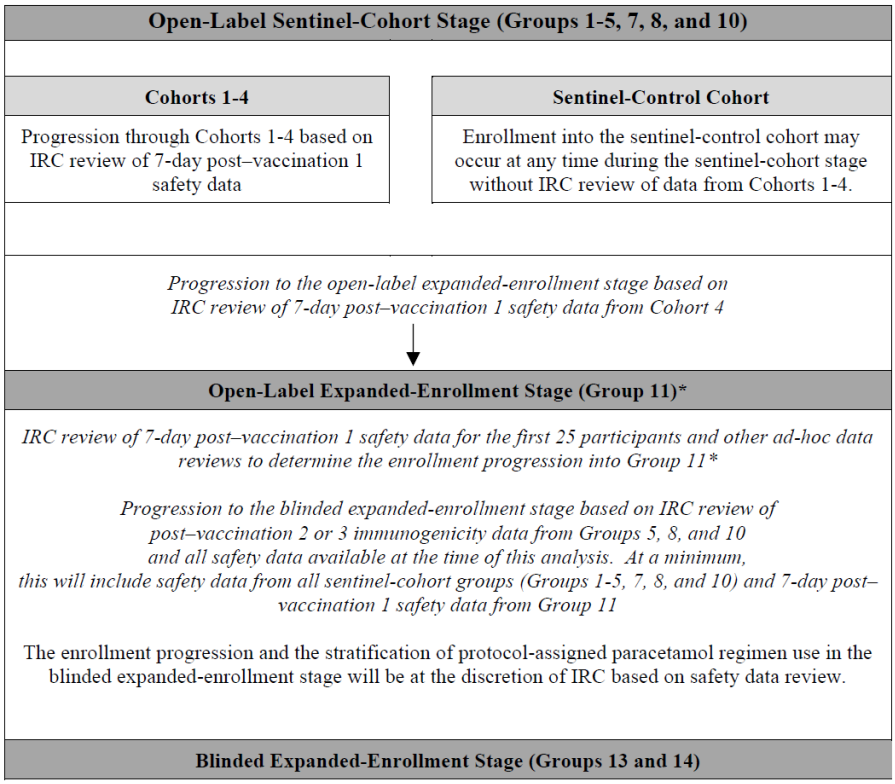
The sentinel-cohort stage comprised 5 cohorts (Cohorts 1 to 4 and a sentinel-control cohort) and 8 groups based on age, protocol-assigned paracetamol use, and vaccines to be administered:

- Cohort 1:

    - Group 1: infants 6 months of age will receive Men ABCWY with PLP
- Cohort 2:
    - Group 2: infants 6 months of age will receive MenABCWY without PLP
    - Group 3: infants 2 months of age will receive 60 µg of bivalent rLP2086 (Trumenba) and Nimenrix with PLP or SLP
- Cohort 3:
    - Group 4: infants 2 months of age will receive 60 µg of bivalent rLP2086 and Nimenrix without PLP
    - o Group 5: infants 2 months of age will receive 120 µg of bivalent rLP2086 and Nimenrix with PLP
- Cohort 4:
    - Group 7: infants 2 months of age will receive MenABCWY with SLP (the exact schedule of the protocol-assigned paracetamol regimen will be at the discretion of the IRC, may be subject to change on an ongoing basis as data become available, and will be described in the protocol-assigned paracetamol dosing instructions).
- Cohort 5:
    - Group 8: infants 2 months of age will receive Bexsero and Nimenrix with PLP
    - Group 10: infants 2 months of age will receive Bexsero and Nimenrix without PLP

The open-label expanded-enrollment stage included 1 additional treatment group (Group 11) that will receive MenABCWY and TLP as treatment only if fever or other reactogenicity symptoms arise within 48 hours after primary series vaccinations (if no symptoms are experienced, no paracetamol will be given).

Figure 1. Planned Study Progression Flowchart



* The decision to terminate this study was made after only 12 participants were enrolled into Group 11.

Assessor's comment

Only immunogenicity results from Group 3, 4 and 5 are discussed. In these groups Trumenba, as either half a dose or full dose, was administered concomitantly with Nimenrix.

For safety, Groups 1 ,2, 3, 4, 5, 7 and 11 are taken into consideration as Trumenba was part of the MenABCWY vaccine.

The design of the study is described below, however, no assessment of the adequacy of the trial design is provided as the current trial was not performed to assess the overall benefit/risk profile of Trumenba. The current assessment focusses on the study results with a potential impact on the benefit/risk, the Summary of Product Characteristics (SmPC) and/or Risk Management Plan (RMP) of Trumenba.

Study participants

Healthy male and female participants 2 months or 6 months of age with a body weight ≥4 kg at the time of randomisation and whose parent(s)/legally acceptable representative (LAR) who could provide written informed consent and in the opinion of the investigator, could and would comply with the requirements of the protocol (e.g., scheduled visits, laboratory tests, study procedures) were included in the study.

Exclusion criteria included previous preterm birth, previous anaphylactic reaction to any vaccine or vaccine-related component, prior adverse reaction to paracetamol, vaccination with any meningococcal vaccine, a known or suspected disorder of the immune system that would have prevented an immune response to the vaccine, significant neurological disorders or neuroinflammatory conditions.

Assessor's comment

Of note, Trumenba is not indicated for use in infants 2 months and 6 months of age.

The population enrolled in the clinical study consisted of healthy, term-born infants. Considering this study was designed to investigate the safety and immunogenicity of the pentavalent meningococcal vaccine MenABCWY in this young population, this is considered acceptable.

Treatments

MenABCWY, 60 µg bivalent rLP2086, 120 µg bivalent rLP2086, Bexsero, and Nimenrix were administered on as 2 primary doses and 1 booster dose. The doses were administered on Day 0 (Visit 1), Month 2 (Visit 3) and Month 6 (Visit 5).

Prevenar 13 and Vaxelis were concomitantly administered to all sentinel-cohort and expanded-enrollment participants during primary vaccinations. Participants 6 months of age received Prevenar 13 and Vaxelis at 6 months of age (Visit 1). Participants 2 months of age received Prevenar 13 and Vaxelis at 2 and 4 months of age (Visits 1 and 3).

Paracetamol

- PLP regimen (Groups 1, 3, 5, 8, and 14): the first dose of PLP were to be administered orally within 30 minutes before the administration of MenB vaccines. Two additional doses of PLP were provided to parent(s)/legal guardian to administer to the participant at 4- to 6-hour intervals on Day 1 following each primary vaccination. In 2-month-old participants receiving rLP2086-containing vaccines in Group 3 and 5, if fever persisted despite administration of 3

doses of PLP, additional paracetamol doses should be given for up to 48 hours after vaccination.

- SLP Regimen (Groups 7, 11, and 13): the first dose of paracetamol was to be administered orally by parent(s)/legal guardian no later than 8 hours after each primary vaccination or earlier if fever or other reactogenicity symptoms arise and require treatment. Parent(s)/legal guardian would continue administering paracetamol for a certain number of doses as described in the protocol-assigned paracetamol dosing instructions. The initial regimen required administration of 4 doses every 4 to 6 hours with an optional fifth dose if symptoms persisted, but this regimen might be adjusted at the discretion of the IRC based on ongoing review of the safety data.
- TLP Regimen (Groups 11, 13, and 14): the first dose of paracetamol was to be administered orally by parent(s)/legal guardian only when fever or other reactogenicity symptoms arise and require treatment (if no symptoms were experienced, no paracetamol would be given). Parent(s)/legal guardian would continue administering paracetamol for a certain number of doses as described in the protocol assigned paracetamol dosing instructions. The initial regimen required administration of 4 doses every 4 to 6 hours with an optional fifth dose if symptoms persist, but this regimen might be adjusted at the discretion of the IRC based on ongoing review of the safety data.

Assessor's comment

No posology is available for Trumenba in infants 2 months and 6 months of age.

The treatment regimen used in the study was in line with the posology of Bexsero, which can be used in infants 2 to 6 months of age. In the SmPC of Bexsero it is mentioned that prophylactic use of paracetamol reduces the incidence and severity of fever without affecting immunogenicity. Therefore, the treatment regimen used in the study can be considered acceptable.

Objective(s) and Outcomes/endpoints

The immunogenicity objectives, estimands and endpoints related to Trumenba are presented in Table 3. The study included more objectives, estimands and endpoints not related to Trumenba. However, these have not been included in this assessment report.

Table 3. 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**
Primary Immunogenicity Objective:	Primary Immunogenicity Estimands:	Primary Immunogenicity Endpoints:	
To describe the immune response for MenB induced by 60 µg and 120 µg of bivalent rLP2086 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 or combination: Groups 3+4 (60 µg bivalent rLP2086 recipients) Group 5 (120 µg bivalent rLP2086 recipients) The percentage of participants achieving an hSBA titer ≥ LLOQ for each of the MenB 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: The percentage of participants achieving an hSBA titer ≥ LLOQ for each of the MenB test strains 1 month after the booster vaccination.	hSBA titer for each of the MenB test strains (TBD).	Post-booster blood draws were not performed and as such post-booster immunogenicity data are not reported for Group 4 and Group 5.
Secondary Immunogenicity Objective:	Secondary Immunogenicity Estimands:	Secondary Immunogenicity Endpoints:	
To further describe the immune response for MenB induced by 60 µg and 120 µg of bivalent rLP2086 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 or combination: Groups 3+4 (60 µg bivalent rLP2086 recipients) Group 5 (120 µg bivalent rLP2086 recipients) hSBA GMTs for each of the MenB 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 MenB test strains 1 month after the booster vaccination.	hSBA titer for each of the MenB test strains (TBD).	Post-booster blood draws were not performed and as such post-booster immunogenicity data are not reported for participants in Group 4 and Group 5.
GMT: geometric mean titer; hSBA: serum bactericidal assay using human complement; LLOq: lower limit of quantification; MenB: *Neisseria meningitidis* serogroup B; TBD: to be determined			

Assessor's comment

The immune response for MenB was to be described in terms of percentage of participants achieving an hSBA titer ≥ LLOQ and hSBA GMTs for each of the MenB test strains 1 month after primary vaccination 2 and after the booster dose. The test strains reported to be tested in the Statistical Analysis Plan (SAP) were A22 and B44 (tested together) and A12, A29, B16, B24 and B44.

No justification for the choice of the test strains was provided. In the SmPC for Trumenba, the following 4 test strains were the primary test strains: A22, A56, B24 and B44. In addition, 10 additional strains were tested (A06, A07, A12, A15, A19, A29, B03, B09, B15, B16), to investigate the breadth of the response to different MenB strains. In the current study, only a few of the strains were tested without any justification on the strains chosen.

Sample size

The sample size for the open label sentinel cohort and expanded enrolment stage of the study was not based on any hypothesis-testing criteria. The study aimed to have a sufficient number of participants in order to describe the safety and the immunogenicity.

The probability of observing at least 1 occurrence of any Adverse Event (AE) for true event percentages between 0.1% and 5.0%, when MenABCWY is administered to 25, 50, 110, or 150 participants, is displayed in Table 4.

Table 4. Probability of observing at least 1 event by assumed true event rates

Assumed True Event Percentage	Probability (N=25)	Probability (N=50)	Probability (N=110)	Probability (N=150)
0.1%	0.02	0.05	0.10	0.14
0.5%	0.12	0.22	0.42	0.53
1.0%	0.22	0.39	0.67	0.78
2.0%	0.40	0.64	0.89	0.95
5.0%	0.72	0.92	>0.99	>0.99

Assessor's comment

No hypothesis testing was underlying the sample size determination. The probability of observing an AE is low, with only the most common AEs being able to be detected.

Randomisation and blinding (masking)

Allocation (randomisation) of participants to vaccine groups proceeded through the use of an IRT system (IWR) that is 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 identification and password, the protocol number, and the participant number. The site personnel were then 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 Case Report Form (CRF). The confirmation report must be stored in the site's files.

The study specific IRT reference manual and investigational product (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. Study intervention was to be dispensed at the study visits summarised in the Schedule of Activities (SoA).

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

Assessor's comment

In group 3, 4 and 5, Trumenba, as either half a dose or full dose, and Nimenrix were administered in an open label fashion. However, assignment occurred via IRT without involvement of the investigator. Blinding could only impact safety assessment.

Statistical Methods

For each of the MenB test strains, the percentages of participants achieving an hSBA titer ≥ LLOQ for group combination 3+4 and Group 5 at 1 month after the booster vaccination was calculated. The analysis at 1 month after the booster vaccination was based on the post–booster vaccination evaluable population.

Exact 2-sided 95% Confidence Interval (CIs) for the percentages was provided using the Clopper-Pearson method. Supportive analyses were performed based on the post–primary vaccination 2 modified Intention-To-Treat (mITT) population for post–primary vaccination 2 results, and the post–booster vaccination mITT population for post-booster results. Participants were summarised according to the vaccine group to which they were randomised. Missing serology data was not imputed.

For each of the MenB test strains, the hSBA GMTs for group combination 3+4 and Group 5 at 1 month after primary vaccination 2 and after the booster vaccination will be calculated.

Analysis sets

For purposes of analysis, the following populations were defined:

Population	**Description**
Enrolled	All participants who sign the informed consent document (ICD).
Randomly assigned to investigational product	All participants who are assigned a randomisation number in the IRT system.
Post–primary vaccination 2 evaluable	All randomised participants who were eligible through Visit 4, received the investigational products at Visits 1 and 3 as randomised, had blood drawn for assay testing within the required time frame at Visit 4 (1 month after primary vaccination 2 [window 28-42 days]), had at least 1 valid and determinate MenA, MenC, MenW, MenY, or MenB assay result at Visit 4, had received no prohibited vaccines or treatment through Visit 4, and had no important protocol deviations through Visit 4. An important protocol deviation is a protocol deviation that, in the opinion of the sponsor's global medical monitor, would materially affect assessment of immunogenicity, e.g., participant receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine.
Post–booster vaccination evaluable	All randomised participants who were eligible through Visit 6, received the investigational products following the vaccination series at Visits 1, 3, and 5 as randomised, had blood drawn for assay testing within the required time frame at Visit 6 (1 month after the booster vaccination [window 28-42 days]), had at least 1 valid and determinate MenA, MenC, MenW, MenY, or MenB assay result at Visit 6, had received no prohibited vaccines or treatment through Visit 6, and had no

	important protocol deviations through Visit 6. An important protocol deviation is a protocol deviation that, in the opinion of the sponsor's global medical monitor, would materially affect assessment of immunogenicity, e.g., participant receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine.
Post–primary vaccination 2 modified-intent-to-treat	All participants who received at least 1 primary series study vaccination and have at least 1 valid and determinate MenA, MenC, MenW, MenY, or MenB assay result available at Visit 4.
Post–booster vaccination modified-intent-to-treat	All participants who received the booster study vaccination and have at least 1 valid and determinate MenA, MenC, MenW, MenY, or MenB assay result available at Visit 6.

Assessor's comment

No hypothesis testing was predefined.

Results

Participant flow

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-enrollment stage. As a result of early study termination, the majority of participants did not complete the study. The number of randomised participants was 326. The number of participants within the post-Vaccination mITT population was 216 and within the post-Primary Vaccination 2 evaluable immunogenicity population was 195. The number of participants in the overall safety population was 325.

Table 5. Participant flow

	Group 3 (2 months) 60 µg rLP2086 + Nimenrix + PLP/SLP	**Group 4 (2 months) 60 µg rLP2086 + Nimenrix**	**Group 5 (2 months) 120 µg rLP2086 + Nimenrix + PLP**
	N[a] (%)	N[a] (%)	N[a] (%)
Randomised	39	17	50
Withdrawn before vaccination	0	1 (5.9)	0
Vaccinated			
Vaccination 1	39 (100.0)	16 (94.1)	50 (100.0)
Vaccination 2	23 (59.0)	16 (94.1)	50 (100.0)
Booster vaccination	22 (56.4)	4 (23.5)	9 (18.0)
Primary vaccination phase			
Vaccination phase completed	23 (59.0)	16 (94.1)	50 (100.0)
Withdrawn	16 (41.0)	0	0
Reason for withdrawal			
Protocol deviation	1 (2.6)	0	0
Study termination	14 (35.9)	0	0
Withdrawal by parent/ legal guardian	1 (2.6)	0	0
Primary follow-up phase			
Follow-up completed	22 (56.4)	4 (23.5)	9 (18.0)
Withdrawn	1 (2.6)	12 (70.6)	41 (82.0)
Reason for withdrawal			
Study termination	0	11 (64.7)	38 (76.0)
Withdrawal by parent/ legal guardian	1 (2.6)	1 (5.9)	3 (6.0)
Booster vaccination phase			
Vaccination phase completed	22 (56.4)	0	0
Withdrawn	0	4 (23.5)	9 (18.0)
Reason for withdrawal			
Study termination	0	4 (23.5)	9 (18.0)
Booster follow-up phase			
Follow-up completed	22 (56.4)	0	0
Withdrawn	0	0	0

Assessor's comment

A limited number of participants were exposed to Trumenba: 39 participants receiving the half dose of Trumenba completed the primary vaccination series (with 55 participants receiving at least 1 dose) and the 50 participants receiving the full dose (120 µg) of Trumenba completed the primary vaccination series.

Only 22 participants receiving 60 µg Trumenba (Group 3) received a booster vaccination and completed the booster vaccination phase (including blood draw). In Group 4 and 5 respectively 4 and 9 participants received a booster dose, however, no post-booster blood draw was performed.

Due to the low number of participants receiving Trumenba, any immunogenicity data obtained is limited.

Recruitment

The first subject was enrolled on 26 November 2020. The study terminated on 17 March 2022 (Last participant last visit 15 September 2022).

The study was conducted in 32 sites in Spain, Greece, Germany and Romania.

Baseline data

Demographic characteristics are presented in Table 6.

Table 6. 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.

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.

Assessor's comment

Due to small numbers of participants included in Groups 3, 4 and 5 differences in the population are present. The most prominent difference is the percentage of non-hispanic/non-latino participants in Group 5, which is 81.1% compared to 41.7% and 50.0% in Groups 3 and 4 respectively.

Number analysed

The proportion of participants in the post-Primary Vaccination 2 mITT population ranged from 40.0% to 100% of randomised participants across all groups, and 59% to 100% in Groups 3, 4 and 5. The proportion of participants in the post-Primary Vaccination 2 evaluable immunogenicity population ranged from 36.0% to 90.0%, and 53.8% to 90% in Groups 3, 4 and 5. In general, the most common reasons for exclusion for the immunogenicity populations were related to study termination.

The proportion of participants in the post-Booster Vaccination mITT population ranged from 40.0% to 53.8%. The proportion of participants in the post-Booster Vaccination evaluable immunogenicity population ranged from 36.4% to 46.2%. The most common reasons for exclusion from the post-Primary Vaccination 2 evaluable immunogenicity population were related to study termination. Due to termination of the study, post-booster blood draws were not performed, and post-booster immunogenicity data were not reported for participants in Group 4 and Group 5.

Table 7. Immunogenicity Populations by Group

	Group 3 (2 months) 60 µg rLP2086 + Nimenrix + PLP/SLP	**Group 4 (2 months) 60 µg rLP2086 + Nimenrix**	**Group 5 (2 months) 120 µg rLP2086 + Nimenrix + PLP**
	N[a] (%)	N[a] (%)	N[a] (%)
Randomised[b]	39	17	50
Post-primary vaccination 2 mITT population	23 (59.0)	15 (88.0)	50 (100.0)
Excluded from post-primary vaccination 2 mITT population	16 (41.0)	2 (11.8)	0
Post-primary vaccination 2 evaluable population	21 (53.8)	14 (82.4)	45 (90.0)
Excluded from post-primary vaccination 2 evaluable population	18 (46.2)	3 (17.6)	5 (10.0)
Reason for exclusion			
Did not maintain eligibility	16 (41.0)	1 (5.9)	0
Did not receive study intervention at Visits 1 and 3 as randomised	18 (46.2)	1 (5.9)	0
Did not have blood draw within 28-42 days after vaccination at Visit 4	16 (41.0)	1 (5.9)	2 (4.0)
Did not have valid and determinate MenACWY or	16 (41.0)	2 (11.8)	0

	Group 3 (2 months) 60 µg rLP2086 + Nimenrix + PLP/SLP	Group 4 (2 months) 60 µg rLP2086 + Nimenrix	Group 5 (2 months) 120 µg rLP2086 + Nimenrix + PLP
Men B assay result after vaccination at Visit 4			
Received prohibited vaccines or treatment	0	0	1 (2.0)
Had important protocol deviations	3 (7.7)	1 (5.9)	3 (6.0)
Post-booster vaccination mITT population	21 (53.8)	0	0
Excluded from post-booster vaccination mITT population	18 (46.2)	17 (100.0)	50 (100.0)
Post-booster vaccination evaluable population	18 (46.2)	0	0
Excluded from post-booster vaccination evaluable population	21 (53.8)	17 (100.0)	50 (100.0)
Reason for exclusion			
Did not maintain eligibility	18 (46.2)	14 (82.4)	42 (84.0)
Did not receive study intervention at Visits 1, 3 and 5 as randomised	19 (48.7)	13 (76.5)	41 (82.0)
Did not have blood draw within 28-42 days after vaccination at Visit 6	19 (48.7)	17 (100.0)	50 (100.0)
Did not have valid and determinate MenACWY or Men B assay result after vaccination at Visit 6	18 (46.2)	17 (100.0)	50 (100.0)
Received prohibited vaccines or treatment	0	0	0
Had important protocol deviations	3 (7.7)	0	3 (6.0)

Abbreviations: Mo = months of age; mITT = modified intent-to-treat; PLP = prophylactic liquid paracetamol; SLP = scheduled liquid paracetamol.
a. n = Number of participants with the specified characteristic.
b. The values in this row are used as the denominators for percentage calculations.

Assessor's comment

The MAH claimed that the majority of reasons for exclusion are linked to study termination, however, the relationship between study termination and reasons for exclusion mentioned in the Clinical Study Report (CSR) is not immediately clear. Upon a request for clarification, the MAH stated the following:

- For Post–primary Vaccination 2 evaluable immunogenicity population:

o Group 3: 14 out of 18 participants excluded from this population were due to study termination;

o Group 7: 23 out of 32 participants excluded from this population were due to study termination;

o Groups 4, 5, 8, and 10: in these groups there were no exclusions due to study termination; the overall percentage of participants excluded was low (ranging from 10.0% to 17.6%).

- For Post–booster vaccination evaluable immunogenicity population:

o Group 3: 14 out of 21 participants excluded from this population were due to study termination;

o Group 4: 15 out of 17 participants excluded from this population were due to study termination;

o Group 5: 47 out of 50 participants excluded from this population were due to study termination;

o Group 7: 43 out of 50 participants excluded from this population were due to study termination;

o Group 8: 29 out of 32 participants excluded from this population were due to study termination;

o Group 10: 29 out of 35 participants excluded from this population were due to study termination.

Further, the MAH clarified that for the majority of cases "did not maintain eligibility based on criteria…" resulted from the study discontinuation. In fact, many randomised participants would have been excluded from the different analysis populations due to the unavailability of a blood drawn for assay testing within the required time frame around a certain visit and the absence of valid and determinate assay results for certain visits which is a direct result of the study being terminated.

Efficacy results

The proportion of participants who achieved an hSBA titer ≥ LLOQ was generally similar in the groups that received 60 µg bivalent rLP2086 + Nimenrix (with/without PLP/SLP) (Groups 3+4) and 120 µg bivalent rLP2086 + Nimenrix + PLP (Group 5) for PMB80 (A22) and PMB2707 (B44), see Table 8.

Table 8. Number (%) of Participants With hSBA Titer ⩾ LLOQ for MenB Test Strains 1 Month After Primary Vaccination 2 – Post-primary Vaccination 2 Evaluable Immunogenicity Population – Primary Endpoint

	Group 3+4 (2 Mo; 60 µg rLP2086 + Nimenrix with/without PLP/SLP	**Group 5 (2 Mo; 120 µg rLP2086 + Nimenrix w PLP**
MenB strain (variant)	N[a] n[b] (%; 95% CI[c])	N[a] n[b] (%; 95% CI[c])
PMB80 (A22)	30 14 (46.7; 28.3-65.7)	44 21 (47.7; 32.5-63.3)
PBM2707 (B44)	35 29 (82.9; 66.4-93.4)	45 44 (97.8; 88.2-99.9)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; MenB = Neisseria meningitidis group B; Mo = months of age.
Note: LLOQ = 1:16 for PMB80 (A22); 1:8 for PMB2707 (B44).
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.

Post-booster blood draws were not performed, and post-booster immunogenicity data are not reported for participants in Group 4 and Group 5.

The proportion of participants in the 60 µg bivalent rLP2086 + Nimenrix +PLP/SLP group post-booster vaccination in the evaluable immunogenicity population achieving an hSBA titer ≥LLOQ was 38.9% (95%CI: 17.3-64.3; 7 participants) for PMB80 (A22) and 83.3% (95% CI: 58.6-96.4; 15 participants) for PBM2707 (B44).

The hSBA GMTs in the 60 µg bivalent rLP2086 + Nimenrix (with/without PLP/SLP) groups (Groups 3+4) and the 120 µg bivalent rLP2086 + Nimenrix + PLP group (Group 5) were generally similar for PMB80 (A22) and PMB2707 (B44).

Table 9. hSBA GMTs for MenB Test Strains 1 Month After Primary Vaccination 2 – Post-primary Vaccination 2 Evaluable Immunogenicity Population – Secondary/Tertiary Endpoint

	Group 3+4 (2 Mo; 60 µg rLP2086 + Nimenrix with/without PLP/SLP	**Group 5 (2 Mo; 120 µg rLP2086 + Nimenrix w PLP**
MenB strain (variant)	N[a] GMT[b] (95% CI[c])	N[a] GMT[b] (95% CI[c])
PMB80 (A22)	30 13.9 (10.8-18.0)	44 15.3 (12.1-19.3)
PBM2707 (B44)	35 13.4 (9.8-18.3)	45 25.0 (19.9-31.4)

Abbreviations: GMT = geometric mean titer; hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; MenB = Neisseria meningitidis group B; Mo = months of age.
Note: LLOQ = 1:16 for PMB80 (A22); 1:8 for PMB2707 (B44).
Note: If the hSBA result is below LLOQ, it will be set to 0.5 × LLOQ for the GMT calculation.
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. Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.

At 1 month after booster vaccination, hSBA GMTs in the 60 µg bivalent rLP2086 + Nimenrix + PLP/SLP group (Group 3) for the PMB80 (A22) MenB test strain was 21.8 (95% CI: 11.1 – 42.6) and for the PMB2707 (B44) MenB test strain 25.4 (95% CI: 12.6 – 51.1).

Assessor's comment

Only information on immunogenicity against 2 MenB strains, A22 and B44, is provided in the CSR.

The immunogenicity data that can be obtained from this study with respect to Trumenba is very limited. Immunogenicity was only measured at baseline, 1 month after vaccination 2 of the primary series and, for an extremely limited number of participants, post booster. Therefore, this study does not provide any information on antibody kinetics and persistence of the antibody response. In addition, the number of participants available with information on Trumenba is limited, with information being available for 39 participants receiving 60 µg Trumenba and 50 receiving 120 µg Trumenba 1 month after the primary vaccination and for only 22 participants receiving 60µg Trumenba after the booster dose.

The responses seen were in general comparable between the 2 doses of Trumenba tested. The proportion of participants achieving hSBA titers ≥LLOQ were low when comparing to the responses seen in participants ≥10 years of age. As immunogenicity after primary vaccination was presented for Group 3+4 together, no clear conclusion can be drawn on the response after the booster vaccination. However, the proportion of participants achieving hSBA titers ≥LLOQ did not seem to increase substantially and the 95% CI of the hSBA titers overlap substantially. This could imply a modest booster capacity of this vaccine in these young infants.

Safety results

Exposure

In total 326 participants were randomised. Across the vaccine groups, up to the point of study termination, all participants received the investigational product to which they were randomised with the following exceptions:

- There were 3 participants in Group 3 who were randomised to receive 60 µg bivalent rLP2086 but received 120 µg bivalent rLP2086 instead due to a medication error. These 3 participants were included in Group 5 for reporting of safety data. Therefore, out of 39 participants randomised in Group 3, 36 (92.3%) received Vaccination 1 as randomised.
- In Group 4, 16 (94.1%) of 17 participants randomised received vaccine as randomised due to 1 participant who withdrew consent before vaccination.

Assessor's comment

Across the different groups, the following number of participants were exposed to any dose of Trumenba:

- Group 1 (6 Mo, MenABCWY + PLP): 23
- Group 2 (6 Mo, MenABCWY): 25
- Group 3 (2 Mo, 60µg Trumenba + Nimenrix + PLP/SLP): 39
- Group 4 (2 Mo, 60µg Trumenba + Nimenrix): 16
- Group 5 (2 Mo, 120µg Trumenba + PLP): 50
- Group 7 (2 Mo, MenABCWY + SLP): 50
- Group 11 (2 Mo, MenABCWY + TLP): 12

In total 215 participants received any dose of Trumenba, with 48 of these participants being 6 months old and 167 being 2 months old.

Based on the number of participants, only frequently occurring adverse events are expected to be observed and assessable.

Local reactions

Local reactions (redness, swelling, and tenderness at the injection site) within 7 days after any vaccination in the primary series are presented in Table 10.

Table 10. Local Reactions Within 7 Days After Primary Vaccinations, by Group – Safety Population – by Protocol-Assigned Paracetamol Regimen

Local reaction	Group 1 (N[a]=23)	Group 2 (N[a]=25)	Group 3 (N[a]=36)	Group 4 (N[a]=16)	Group 5 (N[a]=53)	Group 7 (N[a]=50)	Group 11 (N[a]=12)
	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)
Any[e]	19 (82.6)	20 (80.0)	29 (80.6)	9 (56.3)	38 (71.7)	43 (86.0)	8 (66.7)
Redness[c]	4 (17.4)	12 (48.0)	16 (44.4)	5 (31.3)	18 (34.0)	22 (44.0)	4 (33.3)
Swelling[c]	5 (21.7)	14 (56.0)	11 (30.6)	5 (31.3)	9 (17.0)	26 (52.0)	2 (16.7)
Tenderness at injection site[d]	18 (78.3)	18 (72.0)	23 (63.9)	7 (43.8)	35 (66.0)	41 (82.0)	8 (66.7)

Group 1: 6 months old receiving MenABCWY + PLP; Group 2: 6 months old receiving MenABCWY; Group 3: 2 months old receiving 60µg Trumenba + Nimenrix + PLP/SLP; Group 4: 2 months old receiving 60µg Trumenba + Nimenrix; Group 5: 2 months old receiving 120µg Trumenba + Nimenrix + PLP; Group 7: 2 months old receiving MenABCWY + SLP; Group 11: 2 months old receiving MenABCWY + TLP.
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.
a. 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.
b. n = Number of participants reporting maximum severity of mild, moderate, or severe based on the severity scales.
c. Mild is 0.5 to 2.0 cm, moderate is >2.0 to 7.0 cm, severe is >7.0 cm.
d. Mild = hurts if gently touched, moderate = hurts if gently touched with crying, severe = causes limitation of limb movement.
e. Any local reaction = any tenderness at injection site, any swelling ≥0.5 cm, or any redness ≥0.5 cm.

Local reactions (redness, swelling, and tenderness at the injection site) within 7 days after booster vaccination are presented in Table 11.

Table 11. Local Reactions within 7 Days After Booster Vaccination by Group – Safety Population

Local reaction	Group 1 + 2 (6 Mo, MenABCWY with/without PLP) (N[a]=47)	Group 3 +4 (2 Mo, 60 µg Trumenba + Nimenrix with/without PLP/SLP) (N[a]=23)	Group 5 (2 Mo, 120 µg Trumenba + Nimenrix with PLP) (N[a]=9)
	n[b] (%)	n[b] (%)	n[b] (%)
Any[e]	31 (66.0)	13 (56.5)	7 (77.8)
Redness[c]	14 (29.8)	7 (30.4)	2 (22.2)
Swelling[c]	13 (27.7)	5 (21.7)	1 (11.1)
Tenderness at injection site[d]	26 (55.3)	11 (47.8)	7 (77.8)

Group 1: 6 months old receiving MenABCWY + PLP; Group 2: 6 months old receiving MenABCWY; Group 3: 2 months old receiving 60µg Trumenba + Nimenrix + PLP/SLP; Group 4: 2 months old receiving 60µg Trumenba + Nimenrix; Group 5: 2 months old receiving 120µg Trumenba + Nimenrix + PLP; Group 7: 2 months old receiving MenABCWY + SLP; Group 11: 2 months old receiving MenABCWY + TLP.
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: Participants in the booster vaccination safety population are included in the reporting for Vaccination 3.
Note: Local reactions are summarized only for the left thigh, which is the MenABCWY, Bivalent rLP2086, or Bexsero injection site. One participant in Group 2 received MenABCWY in the right thigh.
a. 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.
b. n = Number of participants reporting maximum severity of mild, moderate, or severe based on the severity scales.
c. Mild is 0.5 to 2.0 cm, moderate is >2.0 to 7.0 cm, severe is >7.0 cm.
d. Mild = hurts if gently touched, moderate = hurts if gently touched with crying, severe = causes limitation of limb movement.
e. Any local reaction = any tenderness at injection site, any swelling ≥0.5 cm, or any redness ≥0.5 cm.

Assessor's comment

In all groups receiving Trumenba the majority of participants experienced a local solicited adverse event during the primary vaccination, with percentages ranging from 56.3% to 86.0%. The most commonly reported local reaction was tenderness at the injection site. The majority of the local solicited adverse events were mild to moderate in intensity and of short duration. No clear increase in occurrence of local adverse events after the second vaccination was observed.

The impact of paracetamol regimen on local reactions appears limited and not consistent across groups. In the 6 months old infants (Group 1 and 2), paracetamol regimen seems to impact redness and swelling, although this is not clear in the 2-month-old infants when comparing Group 3 and 4.

After the booster vaccination, again the majority of participants receiving any dose of Trumenba experienced a local reaction, with tenderness at the injection site being the most commonly reported. The majority of the local solicited adverse events were mild to moderate in intensity and of short duration.

No comparison for paracetamol regimen was made in this group.

The reported local solicited reactions are in line with the adverse events reported in the SmPC for toddlers 1 to <2 years of age.

Systemic reactions

The proportion of participants who reported systemic events within 7 days after any primary vaccination, by protocol-assigned paracetamol regimen is presented in Table 12.

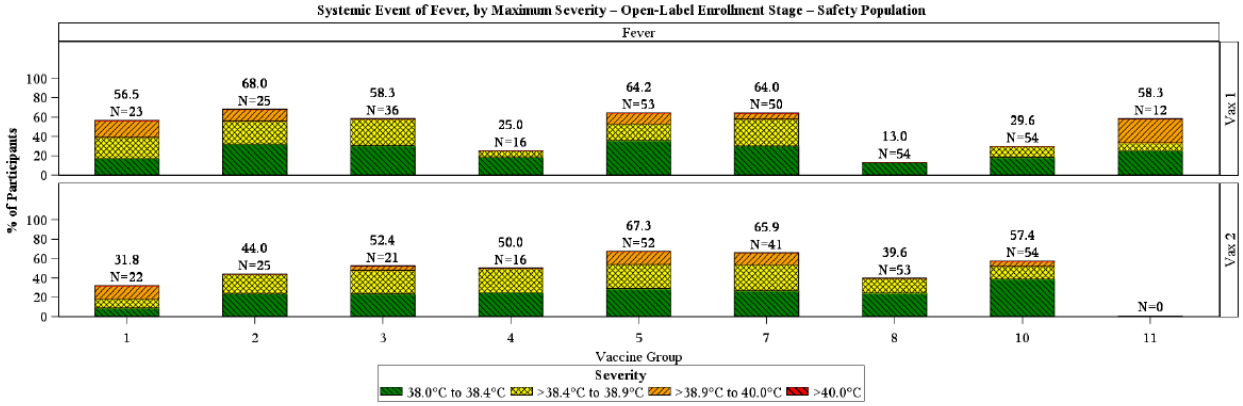
Table 12. Systemic Events Within 7 Days After Primary Vaccinations Visit, by Group – Safety Population – by Protocol-Assigned Paracetamol Regimen

Systemic reaction	Group 1 (N[a]=23)	Group 2 (N[a]=25)	Group 3 (N[a]=36)	Group 4 (N[a]=16)	Group 5 (N[a]=53)	Group 7 (N[a]=50)	Group 11 (N[a]=12)
	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)
Any[f]	22 (95.7)	24 (96.0)	36 (100.0)	16 (100.0)	53 (100.0)	50 (100.0)	12 (100.0)
Fever (≥38°C)	15 (65.2)	18 (72.0)	23 (63.9)	9 (56.3)	42 (79.2)	38 (76.0)	7 (58.3)
Fever (>38.9-40.0°C)	5 (21.7)	3 (12.0)	1 (2.8)	0	12 (22.6)	7 (14.0)	3 (25.0)
Decreased appetite[c]	16 (69.6)	15 (60.0)	21 (58.3)	11 (68.8)	46 (86.8)	38 (76.0)	9 (75.0)
Irritability[d]	21 (91.3)	18 (72.0)	31 (86.1)	14 (87.5)	50 (94.3)	49 (98.0)	12 (100.0)
Drowsiness[e]	18 (78.3)	18 (72.0)	32 (88.9)	12 (75.0)	50 (94.3)	39 (78.0)	10 (83.3)
Use of antipyretic medication[g]	20 (87.0)	24 (96.0)	25 (69.4)	15 (93.8)	50 (94.3)	29 (58.0)	4 (33.3)

Group 1: 6 months old receiving MenABCWY + PLP; Group 2: 6 months old receiving MenABCWY; Group 3: 2 months old receiving 60µg Trumenba + Nimenrix + PLP/SLP; Group 4: 2 months old receiving 60µg Trumenba + Nimenrix; Group 5: 2 months old receiving 120µg Trumenba + Nimenrix + PLP; Group 7: 2 months old receiving MenABCWY + SLP; Group 11: 2 months old receiving MenABCWY + TLP.
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.
a. 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.
b. n = Number of participants reporting maximum severity of mild, moderate, or severe based on the severity scales.
c. Mild = decreased interest in eating; moderate = decreased oral intake; severe = refusal to feed.
d. Mild = easily consolable; moderate = requiring increased attention; severe = inconsolable; crying cannot be comforted.
e. Mild = increased or prolonged sleeping bouts; moderate = slightly subdued interfering with daily activity; severe = disabling not interested in usual daily activity.
f. Any systemic event = any temperature ≥38.0℃, any decreased appetite, any irritability, or any drowsiness.
g. This includes antipyretic medication other than the protocol-assigned paracetamol. Severity is not collected for use of antipyretic or pain medication.

The proportion of participants who reported fever within 7 days after any primary vaccination, by protocol-assigned paracetamol regimen is presented in Figure 2.

Figure 2. Systemic Event of Fever, by Maximum Severity, Within 7 Days After Primary Vaccinations, by Vaccine Group During the Open-Label Enrollment Stage – 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 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.

Systemic events within 7 days after booster vaccination are presented in Table 13.

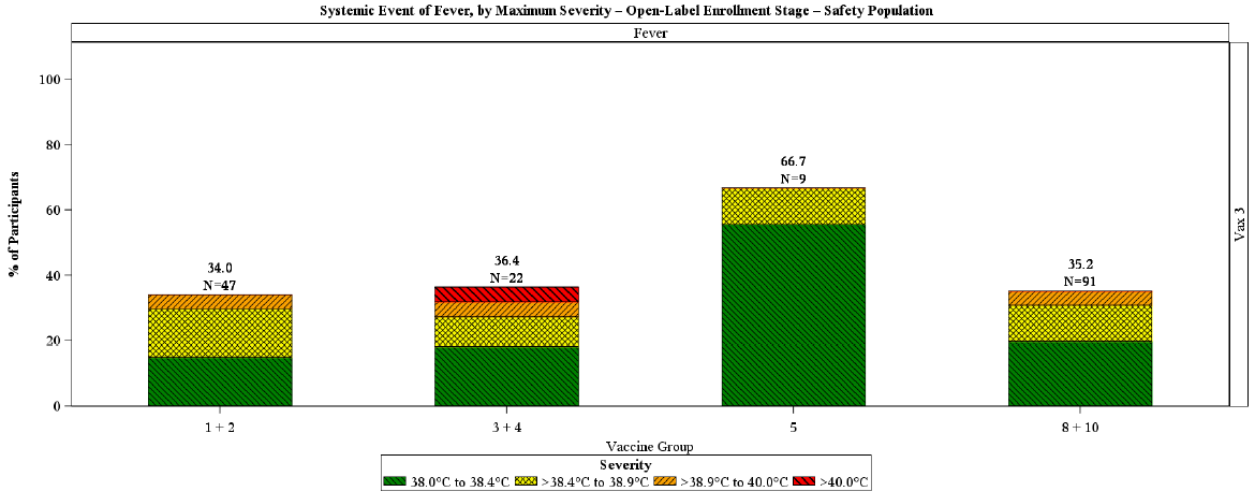
Table 13. Systemic Events Within 7 Days After Booster Vaccination Visit, by Group – Safety Population

Systemic reaction	**Group 1 + 2 (6 Mo, MenABCWY with/without PLP) (N[a]=47)**	**Group 3 +4 (2 Mo, 60 µg Trumenba + Nimenrix with/without PLP/SLP) (N[a]=22/23)**	**Group 5 (2 Mo, 120 µg Trumenba + Nimenrix with PLP) (N[a]=9)**
	n[b] (%)	**n[b] (%)**	**n[b] (%)**
Any[e]	37 (78.7)	21 (91.3)	9 (100.0)
Fever (≥38°C)	16 (34.0)	8 (36.4)	6 (66.7)
Fever (>38.9-40.0°C)	2 (4.3)	1 (4.5)	0
Decreased appetite[c]	22 (46.8)	12 (52.2)	6 (66.7)
Irritability[d]	29 (61.7)	16 (69.6)	6 (66.7)
Drowsiness[e]	20 (42.6)	14 (60.9)	7 (77.8)
Use of antipyretic medication[g]	33 (70.2)	16 (72.7)	5 (55.6)

Group 1: 6 months old receiving MenABCWY + PLP; Group 2: 6 months old receiving MenABCWY; Group 3: 2 months old receiving 60µg Trumenba + Nimenrix + PLP/SLP; Group 4: 2 months old receiving 60µg Trumenba + Nimenrix; Group 5: 2 months old receiving 120µg Trumenba + Nimenrix + PLP; Group 7: 2 months old receiving MenABCWY + SLP; Group 11: 2 months old receiving MenABCWY + TLP.
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.
a. 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.
b. n = Number of participants reporting maximum severity of mild, moderate, or severe based on the severity scales.
c. Mild = decreased interest in eating; moderate = decreased oral intake; severe = refusal to feed.
d. Mild = easily consolable; moderate = requiring increased attention; severe = inconsolable; crying cannot be comforted.
e. Mild = increased or prolonged sleeping bouts; moderate = slightly subdued interfering with daily activity; severe = disabling not interested in usual daily activity.
f. Any systemic event = any temperature ≥38.0℃, any decreased appetite, any irritability, or any drowsiness.
g. This includes antipyretic medication other than the protocol-assigned paracetamol. Severity is not collected for use of antipyretic or pain medication.

The proportion of participants who reported fever within 7 days after booster vaccination is presented in Figure 3.

Figure 3. Systemic Event of Fever, by Maximum Severity, Within 7 Days After Booster Vaccination – Safety Population



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);

Assessor's comment

In all groups receiving Trumenba the vast majority of participants, ≥95%, experienced at least 1 systemic solicited adverse event during the primary vaccination. The most commonly reported systemic reactions were irritability and drowsiness. The majority of the systemic solicited adverse events were mild to moderate in intensity and of short duration (1 to 3 days).

The majority of participants in all groups receiving any dose of Trumenba experienced fever ≥38°C. The percentage of participants experiencing fever >38.9°C to 40.0°C ranged from 0% to 25.0% in all groups. None of the participants experienced fever >40.0°C. Any impact of paracetamol regimen is limited and mainly restricted to fever of 38.0°C-38.4°C. A full dose of Trumenba even with paracetamol led to 58.3% - 79.2% of participants experiencing any fever and 14.0-25.0% of participants experiencing fever >38.9°C to 40.0°C.

The impact of paracetamol regimen on systemic solicited reactions appears limited and not consistent across groups. In addition, no impact on onset or duration of systemic solicited events of paracetamol regimen is observed.

After the booster vaccination, the majority of participants receiving any dose of Trumenba experienced a systemic solicited reaction, with drowsiness and irritability being the most commonly reported. The majority of the local solicited adverse events were mild to moderate in intensity and of short duration.

The percentage of participants reporting any fever after the booster vaccination was lower compared to after the primary vaccination series, ranging from 34.0-66.7%. However, one participant in group 3 reported severe fever >40.0°C.

No comparison for paracetamol regimen was made in this group.

The reported systemic solicited reactions are in line with the adverse events reported in the SmPC for toddlers 1 to <2 years of age.

Related Adverse events

Related AEs reported during the primary vaccination phase by System Organ Class (SOC) and Preferred Term (PT) in the Primary Vaccination 1 and 2 safety population are presented in Table 14. 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.

There were no related AEs reported during the primary vaccination follow-up phase.

Table 14. Related Adverse Events Reported During the Primary Vaccination Phase, by System Organ Class and Preferred Term – Primary Vaccination 1 and 2 Safety Population

Adverse event ***System Organ Class*** **Preferred Term**	**Group 1 (N[a]=23)** **n[b] (%)**	**Group 2 (N[a]=25)** **n[b] (%)**	**Group 3 (N[a]=36)** **n[b] (%)**	**Group 4 (N[a]=16)** **n[b] (%)**	**Group 5 (N[a]=53)** **n[b] (%)**	**Group 7 (N[a]=50)** **n[b] (%)**	**Group 11 (N[a]=12)** **n[b] (%)**
Any event	4 (17.4)	0	2 (5.6)	0	1 (1.9)	7 (14.0)	2 (16.7)
Gastrointestinal disorders	2 (8.7)	0	2 (5.6)	0	0	1 (2.0)	0
Vomiting	2 (8.7)	0	2 (5.6)	0	0	1 (2.0)	0
General disorders and administration site conditions	1 (4.3)	0	0	0	0	4 (8.0)	0
Injection site erythema	0	0	0	0	0	1 (2.0)	0
Injection site swelling	0	0	0	0	0	1 (2.0)	0
Pain	0	0	0	0	0	1 (2.0)	0
Pyrexia	1 (4.3)	0	0	0	0	3 (6.0)	0
Swelling	0	0	0	0	0	1 (2.0)	0
Metabolism and nutrition disorders	1 (4.3)	0	0	0	1 (1.9)	1 (2.0)	2 (16.7)
Decreased appetite	1 (4.3)	0	0	0	1 (1.9)	1 (2.0)	2 (16.7)
Musculoskeletal and connective tissue disorders	0	0	0	0	0	0	2 (16.7)
Pain in extremity	0	0	0	0	0	0	2 (16.7)
Nervous system disorder	0	0	0	0	0	(1 (2.0)	2 (16.7)
Somnolence	0	0	0	0	0	(1 (2.0)	2 (16.7)
Psychiatric disorders	2 (8.7)	0	0	0	1 (1.9)	4 (8.0)	2 (16.7)
Irritability	2 (8.7)	0	0	0	1 (1.9)	4 (8.0)	2 (16.7)
Skin and subcutaneous tissue disorders	0	0	0	0	0	1 (2.0)	0
Erythema	0	0	0	0	0	1 (2.0)	0

Group 1: 6 months old receiving MenABCWY + PLP; Group 2: 6 months old receiving MenABCWY; Group 3: 2 months old receiving 60µg Trumenba + Nimenrix + PLP/SLP; Group 4: 2 months old receiving 60µg Trumenba + Nimenrix; Group 5: 2 months old receiving 120µg Trumenba + Nimenrix + PLP; Group 7: 2 months old receiving MenABCWY + SLP; Group 11: 2 months old receiving MenABCWY + TLP.
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.
a. 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.
b. n = Number of participants reporting maximum severity of mild, moderate, or severe based on the severity scales.

Across the groups that received booster vaccination, related AEs were reactogenicity events (pyrexia and irritability), see Table 15. This can be attributed to reactogenicity events being reported as AEs on the CRF because caregivers missed reporting them in the e-diary or the events required reporting as Medical Administration Errors (MAEs). No related or severe AEs and no Newly Diagnosed Chronic Medical Conditions (NDCMCs) were reported during the booster follow-up phase.

Table 15. Related Adverse Events Reported During the Booster Vaccination Phase, by System Organ Class and Preferred Term – Booster Vaccination Safety Population

Adverse event ***System Organ Class*** **Preferred Term**	**Group 1 + 2** **(6 Mo, MenABCWY with/without PLP)** **(N[a]=47)**	**Group 3 +4** **(2 Mo, 60 µg Trumenba + Nimenrix with/without PLP/SLP)** **(N[a]=24)**	**Group 5** **(2 Mo, 120 µg Trumenba + Nimenrix with PLP)** **(N[a]=11)**
	n[b] (%)	**n[b] (%)**	**n[b] (%)**
Any event	1 (2.1)	2 (8.3)	1 (9.1)
General disorders and administration site conditions	1 (2.1)	2 (8.3)	1 (9.1)
Pyrexia	1 (2.1)	2 (8.3)	1 (9.1)

Group 1: 6 months old receiving MenABCWY + PLP; Group 2: 6 months old receiving MenABCWY; Group 3: 2 months old receiving 60µg Trumenba + Nimenrix + PLP/SLP; Group 4: 2 months old receiving 60µg Trumenba + Nimenrix; Group 5: 2 months old receiving 120µg Trumenba + Nimenrix + PLP; Group 7: 2 months old receiving MenABCWY + SLP; Group 11: 2 months old receiving MenABCWY + TLP.
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.
a. 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.
b. n = Number of participants reporting maximum severity of mild, moderate, or severe based on the severity scales.
c. Mild = decreased interest in eating; moderate = decreased oral intake; severe = refusal to feed.
d. Mild = easily consolable; moderate = requiring increased attention; severe = inconsolable; crying cannot be comforted.
e. Mild = increased or prolonged sleeping bouts; moderate = slightly subdued interfering with daily activity; severe = disabling not interested in usual daily activity.
f. Any systemic event = any temperature ≥38.0℃, any decreased appetite, any irritability, or any drowsiness.
g. This includes antipyretic medication other than the protocol-assigned paracetamol. Severity is not collected for use of antipyretic or pain medication.

Assessor's comment

The number of related unsolicited AEs in each group is low, which is not surprising considering the low number of participants in each group. As only 215 participants received any dose of Trumenba, the probability of observing a common related AE is low, as a related AE that occurs in 1% of participants would only be observed twice.

The majority of related AEs were considered comparable to reactogenicity events. No new safety signal was observed.

Serious Adverse events

SAEs reported during the study, by SOC and PT, are presented in Table 16. The most commonly reported SOC was Infections and infestations and none of the SAEs were considered related to vaccine. There was a higher number of SAEs reported in participants who received 120 µg bivalent rLP2086 + Nimenrix + PLP (Group 5) relative to participants in other vaccine groups, which can be attributed to a higher number of infections reported in this group, none of which were considered related to vaccine.

Table 16. Serious Adverse Events Reported During the Study, by System Organ Class and Preferred Term – Safety Population

System Organ Class **Preferred Term**	**Group 1 (N[a]=23)**	**Group 2 (N[a]=25)**	**Group 3 (N[a]=36)**	**Group 4 (N[a]=16)**	**Group 5 (N[a]=53)**	**Group 7 (N[a]=50)**	**Group 11 (N[a]=12)**
	n[b] (%)	**n[b] (%)**	**n[b] (%)**	**n[b] (%)**	**n[b] (%)**	**n[b] (%)**	**n[b] (%)**
Any Serious adverse event	0	1 (4.0)	1 (2.8)	1 (6.3)	11 (20.8)	5 (10.0)	1 (8.3)
Blood and lymphatic system disorders	0	0	1 (2.8)	0	0	0	0
Lymphadenitis	0	0	1 (2.8)	0	0	0	0
Eye disorders	0	1 (4.0)	0	0	0	0	0
Papilloedema	0	1 (4.0)	0	0	0	0	0
Gastrointestinal disorders	0	0	0	0	1 (1.9)	0	0
Diarrhoea	0	0	0	0	1 (1.9)	0	0
General disorders and	0	0	0	0	0	1 (2.0)	0

System Organ Class **Preferred Term**	**Group 1 (N[a]=23)**	**Group 2 (N[a]=25)**	**Group 3 (N[a]=36)**	**Group 4 (N[a]=16)**	**Group 5 (N[a]=53)**	**Group 7 (N[a]=50)**	**Group 11 (N[a]=12)**
	n[b] (%)	**n[b] (%)**	**n[b] (%)**	**n[b] (%)**	**n[b] (%)**	**n[b] (%)**	**n[b] (%)**
administration site conditions							
Sudden infant death syndrome	0	0	0	0	0	1 (2.0)	0
Infections and infestations	0	0	0	1 (6.3)	7 (13.2)	3 (6.0)	1 (8.3)
Bronchiolitis	0	0	0	1 (6.3)	2 (3.8)	2 (4.0)	0
COVID-19	0	0	0	0	1 (1.9)	0	0
Escherichia urinary tract infection	0	0	0	0	0	1 (2.0)	0
Gastroenteritis bacillus	0	0	0	0	1 (1.9)	0	0
Human herpesvirus 7 infection	0	0	0	0	1 (1.9)	0	0
Meningitis bacterial	0	0	0	0	0	0	1 (8.3)
Respiratory syncytial virus bronchitits	0	0	0	0	1 (1.9)	0	0
Urinary tract infection bacterial	0	0	0	0	1 (1.9)	0	0
Nervous system disorders	0	0	0	0	1 (1.9)	0	0
Myoclonus	0	0	0	0	1 (1.9)	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	0	2 (3.8)	1 (2.0)	0
Bronchospasm	0	0	0	0	2 (3.8)	1 (2.0)	0

Group 1: 6 months old receiving MenABCWY + PLP; Group 2: 6 months old receiving MenABCWY; Group 3: 2 months old receiving 60µg Trumenba + Nimenrix + PLP/SLP; Group 4: 2 months old receiving 60µg Trumenba + Nimenrix; Group 5: 2 months old receiving 120µg Trumenba + Nimenrix + PLP; Group 7: 2 months old receiving MenABCWY + SLP; Group 11: 2 months old receiving MenABCWY + TLP.
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.
a. N = number of participants in the specified group. These values are the denominators for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrences of the specified adverse event. For "Any event" n=Number of participants reporting at least 1 occurrence of any adverse event.

The following unrelated SAEs triggered a protocol-defined stopping rule that resulted in changes in study conduct. Narratives for these SAEs are presented and summarised below:

- A participant who received MenABCWY + SLP (Group 7) died from sudden infant death syndrome (SIDS) 22 days after receiving Vaccination 2. 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 participant enrolled into the 120 µg bivalent rLP2086 + Nimenrix + PLP group (Group 5) developed fever requiring hospitalization 1 day after Vaccination 1. The participant required invasive investigations to explore the cause of the fever, including a lumbar puncture which revealed a white blood cells (WBC) count of 18/mm^3 in the cerebrospinal fluid (CSF). At the time of the initial report and prior to completion of all laboratory testing, the investigator deemed the diagnosis as fever secondary to vaccination. After the participant was discharged from the hospital, a molecular analysis revealed Human Herpes Virus 7 in the blood, but not the CSF. Based on this result the investigator updated the SAE term to Human herpesvirus 7 infection and considered that there was not a reasonable possibility that the Human herpesvirus 7 infection was related to study intervention or clinical trial procedure. The participant received Vaccination 2 but was withdrawn prior to receiving a booster dose due to termination of the study by the sponsor and was followed up for safety.
- A participant enrolled into the 120 µg bivalent rLP2086 + Nimenrix + PLP group (Group 5) and 10 months later 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 and the caregiver was advised to bring the participant to the emergency

department. Subsequently, 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 participant enrolled into the MenABCWY + TLP group (Group 11) developed fever, irritability, vomiting, and was reluctant to eat and was admitted to the hospital within 2 days after Vaccination 1. The participant required invasive investigations to explore the cause of the fever, including a lumbar puncture which revealed 720 leukocytes in the CSF. The investigator concluded that the participant had experienced "meningitis of probable bacterial origin without microbiological isolation". The investigator considered that there was not a reasonable possibility that the event was related to the study paracetamol or clinical trial procedures, but the investigator did not provide a causality assessment for MenABCWY, and the event was managed as if the investigator's assessment was that a reasonable possibility exists that the event was related to study vaccination for reporting purposes. The sponsor considered there was not a reasonable possibility that the event of "meningitis of probable bacterial origin without microbiological isolation" [verbatim term], "meningitis bacterial" [PT] was related to the study intervention since there was no plausible pathophysiological mechanism by which the study intervention would be expected to cause the event. The participant was withdrawn from further vaccination because of study termination by the sponsor and was followed up for safety.

The MAH performed a review of all safety data, including 3 cases (the 2 cases discussed above from Group 5 and Group 11 from this study, and 1 similar case arising from historically performed Study B1971008 in an infant who received 60 µg of bivalent rLP2086). In all 3 cases, infants 2 months of age were admitted to the hospital shortly after vaccinations with bivalent 60 or 120 µg rLP2086 or MenABCWY where evaluations revealed CSF pleocytosis. These 3 cases of CSF pleocytosis in 2-month-old infants prompted a statistical analysis using the background rate of aseptic meningitis in Europe, which showed that it was extremely unlikely that these cases of CSF pleocytosis occurred by chance shortly after vaccination.

Assessor's comment

Overall, administration of Trumenba induces a high frequency of occurrence of fever, especially in the very young infants. It is known that after administration of Trumenba the frequency of occurrence of fever increases with decreasing age. During the current study, after primary vaccination, occurrence of fever >38.9°C-40.0°C was very common, despite prophylactic, schedule and/or therapeutic treatment with liquid paracetamol. If any affect could be observed, paracetamol only seemed to affect frequency of mild fever of ≥38.0°C-38.4°C. The 2 cases presented above in Group 5 and 11, described events of persistent fever with peaks ≥38.5°C, which required invasive investigations to determine the cause of the fever. In both cases CSF pleocytosis was apparent after lumbar puncture. Although in both cases causality of the fever and/or CSF pleocytosis cannot be definitively linked to vaccination, even with the clear temporal association, as other etiologies might play a role. The assessment by the MAH that it was extremely unlikely that the cases of CSF pleocytosis occurred by chance shortly after vaccination is not reassuring. Therefore, the MAH has been requested and has agreed to start a Type II variation within 60 days after the completion of the current procedure, in order to include the data on fever and the serious events of fever requiring clinical and laboratory investigations, including lumbar puncture, in infants 2 months of age to section 4.8 of the SmPC. This is in line with information already presented in section 4.8. In addition, the MAH has indicated to consider the inclusion of the following

sentence is warranted in section 4.2: *Trumenba should not be used in children aged 2 to 6 months because of safety concerns (see section 4.8)*. Especially the high occurrence of fever and fever requiring invasive investigations is considered a safety issue in these young infants. Also in light of the statistical analysis using the background rate of aseptic meningitis identifying that it is extremely unlikely to observe these events so close after vaccination in this very small population.

Upon request, the MAH provided the narratives for all SAEs that occurred during the study per treatment group so that the potential relatedness of these SAEs to vaccination could be reviewed. The conclusions of the MAH on the relatedness of the SAEs was agreed and no new safety findings were identified.

Death

There was one death reported during the study in a participant who received MenABCWY + SLP (Group 7) and was 2 months old at the time of enrolment. The participant died from SIDS 22 days after receiving Vaccination 2. An autopsy determined the cause of death as SIDS in the context of a cardiac anomaly. The investigator considered that there was not a reasonable possibility that the SIDS was related to study intervention or clinical trial procedures.

Assessor's comment

The participant died 22 days after vaccination 2. The autopsy determined the cause of death to be SIDS in the context of a cardiac anomaly. The death was not considered related to the study drug. This can be agreed.

Discontinuation due to AE

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

- A participant enrolled into the Bexsero + Nimenrix + PLP group (Group 8) developed irritability and pyrexia on the day of Vaccination 1, which did not require hospitalization or invasive investigations. The investigator considered that there was a reasonable possibility that the irritability and pyrexia were related to the study intervention.
- A participant enrolled into the MenABCWY + PLP group (Group 1) developed pyrexia and decreased appetite on the day of Vaccination 1, followed by irritability (2 occurrences) on 1 and 4 days after Vaccination 1, none of which required hospitalization or invasive investigations. The investigator considered that there was a reasonable possibility that pyrexia, decreased appetite, and irritability (both occurrences) were related to the study intervention. Per the investigator, constipation could also have been a contributing factor for decreased appetite and irritability.

Assessor's comment

Even though the vaccine is reactogenic, only 1 participant was withdrawn from any of the groups receiving any dose of Trumenba due to an AE. The participant was withdrawn by parents/legal guardians due to AEs of pyrexia, decreased appetite and irritability which were considered related to the study drug administrations. These reactions are all covered in the SmPC.

2.3.3. Discussion on clinical aspects

The study provides very limited data on immunogenicity. This study does not provide any information on antibody kinetics and persistence of the antibody response after vaccination. In addition, the only information presented was on 2 MenB test strains, A22 and B44. Therefore, no conclusions can be drawn on the breadth of protection, which is considered highly relevant especially for MenB vaccines containing meningococcal surface proteins as not all MenB strains contain the genes for the proteins used as vaccine antigen or these proteins might not be expressed on the surface. No justification was provided why these strains were chosen from the 4 primary strains included in the marketing authorisation application (MAA) submission.

The responses seen were overall in general comparable between the 2 doses of Trumenba tested. The immune response generated by the vaccine was considered low when comparing to the responses observed in participants ≥10 years of age. As immunogenicity after primary vaccination was presented for Group 3+4 together, no clear conclusion can be drawn on the response after the booster vaccination.

Trumenba is a highly reactogenic vaccine, especially in infants 2 months of age, with all participants experiencing a solicited local or systemic adverse event. The most frequently reported local adverse event was tenderness at the injection site. The most commonly reported systemic adverse events were irritability and drowsiness. The majority of these events were mild to moderate in intensity and of short duration. The majority of related AEs which were reported in the groups receiving any dose of Trumenba were reactogenicity events. This was expected as the probability of observing a related AE which was more frequent than common was very low due to the small population.

Not all narratives for SAEs could be located, which hampers assessment of relatedness. Upon request, the MAH presented the narratives for all SAEs that occurred during the study per treatment group. Review of these narratives did not result in new safety findings.

Of note, administration of Trumenba induces a high frequency of occurrence of fever, especially in the very young infants. During the current study, after primary vaccination, occurrence of fever >38.9°C-40.0°C was very common, despite use of liquid paracetamol. The 2 SAEs occurring in Group 5 and 11, described events of persistent fever with peaks ≥38.5°C, which required invasive investigations to determine the cause of the fever. In both cases CSF pleocytosis was apparent after lumbar puncture. Although in both cases causality of the fever and/or CSF pleocytosis cannot be definitively linked to vaccination, even with the clear temporal association, as other aetiologies might play a role, the assessment by the MAH that it was extremely unlikely that the cases of CSF pleocytosis occurred by chance shortly after vaccination is not reassuring. Therefore, the MAH was requested to commit to start a Type II variation to include the data on fever and the serious events of fever requiring clinical and laboratory investigations, including lumbar puncture, in infants 2 months of age to section 4.8 of the SmPC. This is in line with information already presented in section 4.8. Within this variation, the MAH has indicated to consider the inclusion of the following sentence is warranted in section 4.2: *Trumenba should not be used in children aged 2 to 6 months because of safety concerns (see section 4.8)*. Especially the high occurrence of fever and fever requiring invasive investigations is considered a safety issue in these young infants. Also, in light of the statistical analysis using the background rate of aseptic meningitis identifying that it is extremely unlikely to observe these events so close after vaccination in this very small population.

3. Request for supplementary information

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

1) The MAH should commit to start a Type II variation to include the data on fever, the serious events of fever requiring clinical and laboratory investigations, including lumbar puncture, and CSF pleocytosis, in infants 2 months of age to section 4.8 of the SmPC.

2) An inclusion of the following sentence in section 4.2 can be foreseen: Trumenba should not be used in children aged 2 to 6 months because of safety concerns (see section 4.8). This update is requested to be included in the Type II variation that should be submitted for section 4.8 (OC 1). The MAH is asked to discuss this further and if not considered warranted, a thorough justification should be provided.

3) The MAH claims that the majority of reasons for exclusion are linked to study termination, however, the relationship between study termination and reasons for exclusion mentioned in Table 12 of the CSR is not immediately clear. The MAH is asked to clarify and to present in the table all exclusions directly linked to study termination in a single category, with additional reasons beneath.

4) The MAH is asked to clarify what is meant by the reason for exclusion "did not maintain eligibility based on criteria up until and including Visit 4/6". The percentage of participants that are in this category is considered very high, up to 84%.

5) Only information on 2 strains, A22 and B44, is provided in the CSR. The MAH is asked to present any information on testing of strains A12, A29, B16, B24 and B44, for which analysis was prespecified in the SAP.

6) In case the testing was not performed the MAH is asked to justify, as this additional information would provide insight into the breadth of protection.

7) The MAH is asked to present the narratives for all SAEs that occurred during the study per treatment group.

The timetable is a 30-day response timetable with clock stop.

MAH responses to Request for supplementary information

Question 1. The MAH should commit to start a Type II variation to include the data on fever, the serious events of fever requiring clinical and laboratory investigations, including lumbar puncture, and CSF pleocytosis, in infants 2 months of age to section 4.8 of the SmPC.

Summary of the MAH's response

The MAH agrees to start a Type II variation as requested. The MAH commits to submit this variation within 60 days of the conclusion of this procedure.

Assessment of the MAH's response

The MAH has agreed to submit a type II variation.

Conclusion

Issue solved.

Question 2. An inclusion of the following sentence in section 4.2 can be foreseen: Trumenba should not be used in children aged 2 to 6 months because of safety concerns (see section 4.8). This update is requested to be included in the Type II variation that should be submitted for section 4.8 (OC 1). The MAH is asked to discuss this further and if not considered warranted, a thorough justification should be provided.

Summary of the MAH's response

The MAH will discuss whether inclusion of the above-mentioned statement is warranted. If considered warranted, the MAH will include an update to SmPC Section 4.2 in the Type II variation mentioned in the response to Comment 1.

Assessment of the MAH's response

An update of section 4.2 as suggested will be discussed in the to be submitted type II variation. This is acceptable.

Conclusion

Issue solved.

Question 3. The MAH claims that the majority of reasons for exclusion are linked to study termination, however, the relationship between study termination and reasons for exclusion mentioned in Table 12 of the CSR is not immediately clear. The MAH is asked to clarify and to present in the table all exclusions directly linked to study termination in a single category, with additional reasons beneath.

Summary of the MAH's response

The MAH appreciates that the relationship between study termination and the reasons for exclusion mentioned in CSR Table 12 may not be immediately clear. Please see Table 17 below which presents the immunogenicity populations by group and clarifies the relationship between study termination and the reasons for exclusion. In this table, the participants that were excluded due to study termination are counted only under the "study termination" row and not under any of the subsequent reasons. Participants that are excluded due to reasons other than study termination may be counted under more than 1 reason. This table is in accord with the statement that the majority of reasons for exclusion are linked to study termination. More specifically:

- For Post–primary Vaccination 2 evaluable immunogenicity population:
    - Group 3: 14 out of 18 participants excluded from this population were due to study termination;
    - Group 7: 23 out of 32 participants excluded from this population were due to study termination;
    - Groups 4, 5, 8, and 10: in these groups there were no exclusions due to study termination; the overall percentage of participants excluded was low (ranging from 10.0% to 17.6%).
- For Post–booster vaccination evaluable immunogenicity population:
    - Group 3: 14 out of 21 participants excluded from this population were due to study termination;
    - Group 4: 15 out of 17 participants excluded from this population were due to study termination;

- Group 5: 47 out of 50 participants excluded from this population were due to study termination;
- Group 7: 43 out of 50 participants excluded from this population were due to study termination;
- Group 8: 29 out of 32 participants excluded from this population were due to study termination;
- Group 10: 29 out of 35 participants excluded from this population were due to study termination.

Overall, the majority of reasons for exclusion are linked to study termination and the proportion of participants excluded due to other reasons was low.

Table 17. 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						
Study termination[c]	14 (35.9)	0	0	23 (46.0)	0	0
Did not maintain eligibility based on criteria up until and including Visit 4	2 (5.1)	1 (5.9)	0	7 (14.0)	1 (1.8)	0
Did not receive study intervention at Visits 1 and 3 as randomized	4 (10.3)	1 (5.9)	0	6 (12.0)	1 (1.8)	0
Did not have blood draw within 28 to 42 days after vaccination at Visit 4	2 (5.1)	1 (5.9)	2 (4.0)	7 (14.0)	6 (10.9)	6 (10.9)
Did not have valid and determinate MenACWY or MenB assay result at Visit 4	2 (5.1)	2 (11.8)	0	7 (14.0)	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)	1 (2.0)	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						
Study termination[c]	14 (35.9)	15 (88.2)	47 (94.0)	43 (86.0)	29 (52.7)	29 (52.7)
Did not maintain eligibility based on criteria up until and including Visit 6	4 (10.3)	2 (11.8)	3 (6.0)	7 (14.0)	1 (1.8)	4 (7.3)
Did not receive study intervention at Visits 1, 3, and 5 as randomized	5 (12.8)	2 (11.8)	3 (6.0)	7 (14.0)	1 (1.8)	4 (7.3)
Did not have blood draw within 28 to 42 days after vaccination at Visit 6	5 (12.8)	2 (11.8)	3 (6.0)	7 (14.0)	2 (3.6)	5 (9.1)
Did not have a valid and determinate MenACWY or MenB assay result at Visit 6	4 (10.3)	2 (11.8)	3 (6.0)	7 (14.0)	3 (5.5)	4 (7.3)
Received prohibited vaccines or treatment	0	0	0	0	0	0
Had important protocol deviations	3 (7.7)	0	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: Immunogenictiy 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.
c. Participants excluded due to termination of the study are counted under this reason and not under subsequent reasons.

Assessment of the MAH's response

The MAH has clarified how the different reasons for exclusions relate to the termination of the study and how then indeed the majority of reasons for exclusion are due to study termination. Also see Q.4.

Conclusion

Issue solved.

Question 4. The MAH is asked to clarify what is meant by the reason for exclusion "did not maintain eligibility based on criteria up until and including Visit 4/6". The percentage of participants that are in this category is considered very high, up to 84%.

Summary of the MAH's response

The reason for exclusion "did not maintain eligibility based on criteria up until and including Visit 4/6" describes those participants that did not continue to meet study eligibility criteria up to the designated blood draw visit and were thus excluded from the evaluable immunogenicity population for that reason. In Table 12 of the CSR, the reason for exclusion "did not maintain eligibility based on criteria up until and including Visit 4/6" also includes the participants who did not continue to meet study eligibility criteria up to the designated blood draw visit because of the study termination.

In Table 17 shown in response to Comment 3 in this document, the number of participants whose continued participation was impacted by study termination is described. Note that participants that were excluded from evaluable population due to study termination are counted only under the "study termination" row and not under any of the subsequent rows describing reasons for exclusion. Therefore, when not taking into account participants whose continued participation was impacted by study termination, the percentage of participants in the category "did not maintain eligibility based on criteria up until and including Visit 4/6" is low, ranging from 0% to 14.0% across the groups. These participants that did not maintain eligibility for reasons other than the study termination were either ineligible when they entered the study or withdrawn from the study prior to the blood draw visit. Among them, only 1 participant from Group 8 (2 Mo, Bexsero + Nimenrix + PLP) withdrew due to adverse event (rendering participant not maintaining eligibility) as detailed in CSR Section 5.2.2.6.

Assessment of the MAH's response

Also see Q.3; the MAH clarified how the high percentage of participants "did not maintain eligibility based on criteria…" results from the study discontinuation. Considering many randomised participants would have been excluded from the different analysis populations due to the unavailability of a blood drawn for assay testing within the required time frame around a certain visit and the absence of valid and determinate assay results for certain visits which is a direct result of the study being terminated.

Conclusion

Issue solved.

Question 5. Only information on 2 strains, A22 and B44, is provided in the CSR. The MAH is asked to present any information on testing of strains A12, A29, B16, B24 and B44, for which analysis was prespecified in the SAP.

Summary of the MAH's response

Section 8.1.2 of the protocol clarifies that only 1 LP2086 subfamily A protein and 1 LP2086 subfamily B protein would be used for the immunogenicity endpoints in this study. As noted in the July 2023 Errata

to the CSR enclosed within this submission, the SAP in CSR Appendix 16.1.9, Section 3.1.1.1, inadvertently listed several MenB test strains (i.e., A12, A29, B16, B24, and B44 [PMB3042]). Due to restrictions regarding the total blood volume allowed to be collected from study participants in this age range, the strains selected for evaluation in Study C3511002 included 2 of the 4 primary MenB test strains that have been used in earlier clinical studies, namely strains that express fHbp variants A22 [PMB80] and B44 [PMB2702]. The strains expressing these variants were selected based on (i) epidemiological relevance; (ii) sequence diversity of the fHbp family of proteins (i.e., 1 variant each from subfamily A and B); and (iii) the objective to evaluate strains that express variants heterologous to antigens included in either Trumenba or Bexsero. As such, and according to the study protocol objectives, there is no information for the strains A12, A29, B16, B24, and B44 [PMB3042] to be presented.

Assessment of the MAH's response

As indicated by the MAH, the protocol stated that MenB serum bactericidal assays would use 2 test strains, 1 expressing an LP2086 subfamily A protein and 1 expressing a subfamily B protein. Strains would be detailed in the SAP prior to the commencement of testing. Strains that express fHbp variants A22 [PMB80] and B44 [PMB2707] were selected. The SAP erroneously stated that MenB test strains included A22 and B44 [PMB2707], and A12, A29, B16, B24, and B44 [PMB3042]). An updated errata document has been submitted to reflect and correct this, stating that the primary MenB test strains in Study C3511002 were only A22 and B44 (PMB2707).

In line with the information in the CSR, it is assumed that the B44 strain is PMB2707 as also listed in the erratum and not PMB2702 as stated in the response to question 5.

Conclusion

Issue solved.

Question 6. In case the testing was not performed the MAH is asked to justify, as this additional information would provide insight into the breadth of protection.

Summary of the MAH's response

Testing of these additional strains was not intended to support the per protocol objectives of the study as described in the response to Comment 5 above.

Assessment of the MAH's response

The clarifications of the MAH are sufficient. It should be noted that it would be preferable to test against a larger array of strains for MenB gain more insight into the breadth of protection. However, this is of no consequence to the current procedure, especially in light of the early termination of the study.

Conclusion

Issue solved.

Question 7. The MAH is asked to present the narratives for all SAEs that occurred during the study per treatment group.

Summary of the MAH's response

Through email correspondence between the MAH contact person and the EMA Procedure Lead dated 30 May 2023, it was clarified that the MAH is requested to present the narratives of all 20 SAEs which

occurred throughout the study among participants in Groups 1, 2, 3, 4, 5, 7, and 11 (i.e., to present the narratives for these SAEs per treatment group). The narratives for 4 out of the 20 SAEs which occurred throughout the study among participants in Groups 1, 2, 3, 4, 5, 7, and 11 were presented in Section 14 of the C3511002 CSR. These 4 narratives are also provided in pages 3 to 17 of Appendix 1 of this response document.

The narratives for the remaining 16 SAEs among 16 participants in Groups 1, 2, 3, 4, 5, 7, and 11 are provided per vaccine group in Appendix 2.

Assessment of the MAH's response

The narratives were provided as requested. Review of the narratives did not identify any new safety signals.

Conclusion

Issue solved.

4. Rapporteur's overall conclusion and recommendation

No clear conclusions can be drawn on immunogenicity of Trumenba in infants 2 months of age based on the current study. The study was terminated due to 2 cases of fever requiring invasive investigations in infants 2 months of age, which both met protocol-defined criteria for a stopping rule. Considering the fact that these cases are considered related to the study vaccination, it is requested to include this information in the SmPC of Trumenba.

☒ Fulfilled:

In view of the available data on serious events of fever requiring clinical and laboratory investigations in infants 2 months of age, 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.