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Human Medicines Division

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006

Trumenba

Meningococcal group B vaccine (recombinant, adsorbed)

Procedure no: EMEA/H/C/004051/P46/018.1

Note

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

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Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	22 May 2023	22 May 2023	☐
☐	CHMP Rapporteur Assessment Report	26 Jun 2023	26 Jun 2023	☐
☐	CHMP members comments	10 Jul 2023	10 Jul 2023	☐
☐	Updated CHMP Rapporteur Assessment Report	13 Jul 2023	n.a	☐
☐	CHMP adoption of conclusions:	20 Jul 2023	20 Jul 2023	☐
☐	Submission	12 Sep 2023	12 Sep 2023	☐
☐	Re-start			☐
☐	CHMP Rapporteur Assessment Report	27 Sep 2023	27 Sep 2023	☐
☐	CHMP members comments	02 Oct 2023	02 Oct 2023	☐
☐	Updated CHMP Rapporteur Assessment Report	05 Oct 2023	n.a	☐
☐	CHMP adoption of conclusions:	12 Oct 2023	12 Oct 2023	☐
☐	Submission	17 Oct 2023	17 Oct 2023	☐
☐	Re-start	18 Oct 2023	18 Oct 2023	☐
☐	CHMP Rapporteur Assessment Report	25 Oct 2023	25 Oct 2023	☐
☐	CHMP members comments	30 Oct 2023	30 Oct 2023	☐
☐	Updated CHMP Rapporteur Assessment Report	06 Nov 2023	n/a	☐
☒	CHMP adoption of conclusions:	09 Nov 2023	09 Nov 2023	☐

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1. Introduction

On 21 April 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 B1971057 "A Phase 3, Randomized, Active-Controlled, Observer-Blinded Study to Assess the Immunogenicity, Safety, and Tolerability of Bivalent rLP2086 When Administered as a 2-Dose Regimen and a First-in-Human Study to Describe the Immunogenicity, Safety and Tolerability of a Bivalent rLP2086-Containing Pentavalent Vaccine (MenABCWY) in Healthy Subjects ≥10 to <26 Years of Age)" was part of a clinical development program.

During the Marketing Authorisation Application (MAA) procedure, the data in support of the 2-dose schedule was limited. The data on the 2-dose schedule was obtained from a single phase 2 study, B1971012, a randomised, single-blind, multicentre trial conducted in Europe comparing the safety and immunogenicity of Trumenba administered using various 2- and 3-dose schedules performed using subjects 11 to 18 years of age. A post-marketing commitment was made to the Food and Drug Administration (FDA) to verify and describe the clinical benefit of a 2-dose schedule. Study B1971057 was designed for this purpose. Study B1971057 was comprised of two stages:

- Stage 1 was the observer-blinded primary vaccination series phase that was designed to evaluate the safety profile and immunogenicity of a MenABCWY and Trumenba (bivalent rLP2086) 2-dose primary vaccination series (0 and 6 month). The MAH submitted the B1971057 Stage 1 interim clinical study reports (CSR) on 08 September 2020 as part of Type II variation procedure EMEA/H/C/004051/II/0032 to include 2-dose data in the Trumenba SmPC. This was assessed previously.

- Stage 2 of this study was an open-label and evaluated the immune-persistence of MenABCWY and bivalent rLP2086 up to 48 months after completion of the primary vaccination series and the immunogenicity and safety of a booster dose administered 48 months after completion of the primary vaccination series.

The current assessment focusses on the Stage 2 study results with a potential impact on the benefit risk (BR), SmPC and/or risk management plan (RMP) of bivalent rLP2086. Information related to either Stage 1 or the pentavalent vaccine is not assessed or discussed.

2.2. Information on the pharmaceutical formulation used in the study

Bivalent rLP2086 is a 0.5-mL dose supplied as a prefilled syringe and formulated to contain 60 µg each of a purified subfamily A and a purified subfamily B rLP2086 protein, 0.15 M sodium chloride, 2.8 molar ratio polysorbate 80, and 0.25 mg of Al3+ as aluminum phosphate (AlPO4) in 10 mM histidine-buffered saline at pH 6.0.

The manufacturing lots used are listed in Table 1:

Table 1. Investigational Product Lot Numbers – Stage 2

Investigational Product	Manufacturer	Vendor Lot Number (Manufacturer)	Lot Number[a] (Pfizer)
Bivalent rLP2086	Pfizer	CL3237	20-000165

		DA4348	20-003058	

a. Lot number assigned to the investigational product by Pfizer Global Clinical Supply.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted an interim report and a final report for:

- Study B1971057 "A Phase 3, Randomized, Active-Controlled, Observer-Blinded Study to Assess the Immunogenicity, Safety, and Tolerability of Bivalent rLP2086 When Administered as a 2-Dose Regimen and a First-in-Human Study to Describe the Immunogenicity, Safety and Tolerability of a Bivalent rLP2086-Containing Pentavalent Vaccine (MenABCWY) in Healthy Subjects ≥10 to <26 Years of Age".

2.3.2. Clinical study B1971057

Description

This study consisted of two stages: stage 1 (Visit 1 through 6, up until 12-18 months after first vaccination), which evaluated the 2-dose schedule for Trumenba and stage 2 (Visit 7 through 12, starting approximately 18 months after first vaccination up until 60 months after the first vaccination), which assessed the duration of the immune response and the response to a booster dose. Only the data for Stage 2 is included in the submission for the current procedure.

Methods

Stage 2 of this study was open-label and evaluated the immunopersistence of bivalent rLP2086 + MenACWY-CRM up to 48 months after completion of the primary vaccination series and the immunogenicity and safety of a booster dose administered 48 months after completion of the primary vaccination series.

The design of the study is presented in Table 2:

Table 2. Study B1971057 Stage 2 study design

		Antibody Persistence	Booster Vaccination	Postbooster Blood Draw	Safety Telephone Call
	Approximate Month	18-42	54	55	60
	Visit Number	7-9	10	11	12
ACWY-Naïve Subjects	Group 1 (n ~132)		MenABCWY		
	Group 2 (n ~65)		Bivalent rLP2086 + MenACWY-CRM		
ACWY-Experienced Subjects[a]	Group 3 (n ~132)		MenABCWY		
	Group 4 (n ~65)		Bivalent rLP2086 + MenACWY-CRM		
	Blood Draw for Serum Collection	20 mL × 3[b]	20 mL	20 mL (or up to 100 mL in subset)	

a. Subjects who received a vaccine containing 1 or more ACWY serogroups at least 4 years prior to enrollment were considered ACWY-experienced.
b. 20 mL at Months 18, 30, and 42.

Assessor's comment

Only immunogenicity results from Group 2 and 4 will be discussed. In these groups Trumenba was administered concomitantly with MenACWY-CRM (Menveo).

For safety, Groups 1, 2, 3, and 4 will be taken into consideration as Trumenba was part of the MenABCWY vaccine.

The current assessment focusses on the study results with a potential impact on the BR, SmPC and/or RMP of Trumenba.

Study participants

Both ACWY-naïve and ACWY-experienced healthy participants ≥10 to <26 years of age were enrolled in this study.

Key exclusion criteria included previous vaccination with any meningococcal group B vaccine or any purely polysaccharide (nonconjugate) meningococcal vaccine; previous vaccination with >1 dose of a vaccine containing 1 or more ACWY group or previous vaccination with 1 dose of vaccine containing 1 or more ACWY group <4 years prior to date of randomisation. In addition, any known or suspected defect of the immune system, history of microbiologically proven disease caused by *N. meningitidis* or *N. gonorrhoeae*, significant neurological disorder, any neuroinflammatory or autoimmune condition or concomitant use of an unlicensed allergen immunotherapy or use of a licensed allergen immunotherapy and not on a stable maintenance dose excluded a participant.

Assessor's comment

In- and exclusion criteria were already assessed as part of Type II variation procedure EMEA/H/C/004051/II/0032.

The criteria were deemed appropriate. The population enrolled in the clinical study consists of healthy individuals from the age of 10 years to <26 years. This is the population for which Trumenba is indicated.

Treatments

For this study, the investigational products were Trumenba, MenABCWY (consisting of MenACWY-TT and bivalent rLP2086), MenACWY-CRM (Menveo) and placebo. Each intervention was administered as a 0.5-mL dose in the upper deltoid muscle of the left or right arm.

As the study interventions were different in physical appearance, the study vaccine syringes were administered in a manner that prevented the study subjects from identifying the vaccine type based on its appearance.

During Stage 2, study intervention was administered at visit 10, approximately 48 months after the primary vaccination.

Assessor's comment

Subjects received the recommended dose for both vaccines as per SmPC. Trumenba was administered 6 months apart as recommended in the SmPC for the 2-dose schedule.

Objective(s)

The following are objectives for Stage 2 relevant to Trumenba.

Key immunogenicity objectives:

- To describe the immune response induced by bivalent rLP2086, as measured by hSBA performed with 4 primary MenB test strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, at blood sampling time points prior to the booster vaccination (Stage 2). Blood sampling time points prior to the booster dose are 12, 24, 36, and 48 months after completion of the primary vaccination series.
- To describe the immune response induced by bivalent rLP2086, as measured by hSBA performed with 4 primary MenB test strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, measured 1 month after the booster vaccination in Groups 2 and 4.
- To further describe the immune response (booster GMTs) induced by bivalent rLP2086, as measured by hSBA performed with 4 primary MenB test strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, measured 1 month after the booster vaccination in Groups 2 and 4.

Safety objective:

- To describe the safety profile of bivalent rLP2086, as measured by local reactions, systemic events, adverse events (AEs), serious adverse events (SAEs), newly diagnosed chronic medical conditions, medically attended AEs, and immediate AEs, after the booster vaccination.

Assessor's comment

The immunogenicity objectives assessed both the persistence of the immune response and the immune response after the booster by measuring hSBA titers for the 4 primary MenB strains. This is considered acceptable.

Combining Group 2 and 4 is acceptable as the groups only differed in ACWY-experience, with group 2 being ACWY-naïve and group 4 being ACWY-experienced. This is not considered to affect the response to MenB vaccine.

The safety objectives are acceptable.

Outcomes/endpoints

Four primary MenB test strains, PMB80 (A22), PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44), each expressing a factor H binding protein (fHBP) variant heterologous to the vaccine component antigens, were used in the hSBAs for determination of the immunogenicity endpoints in this study. The lower limit of quantification (LLOQ) was 1:16 for PMB80 (A22), 1:8 for PMB2001 (A56), 1:8 for PMB2707 (B44), and 1:8 for PMB2948 (B24).

The following endpoints were reported:

- Proportions of subjects with hSBA titers ≥ LLOQ for each of the 4 primary MenB test strains at Visits 7, 8, 9, 10, and 11.
- hSBA geometric mean titers (GMTs) for each of the 4 primary MenB test strains at Visit 11.

Assessor's comment

The persistence data is limited to the proportion of subjects with hSBA titers ≥LLOQ at several different time points after vaccination and hSBA GMT titers will not be determined. The immunogenicity

endpoint of hSBA titer ≥ LLOQ for each of the 4 primary MenB test strains is considered clinically relevant as an hSBA titer of ≥1:4 is the presumptive correlate of protection.

After the booster dose only percentage of participants with hSBA titer ≥ LLOQ and GMTs are measured. Determination of 4-fold rise was not included. The 4-fold rise could have been used to further assess the immune response to the booster dose. However, for the current procedure the measured endpoints are considered sufficient.

Sample size

Subjects from both the ACWY-naïve and ACWY-experienced strata, approximately 132 from each of Groups 1 and 3 and approximately 65 from each of Groups 2 and 4, were planned to participate in Stage 2.

Assessor's comment

The sample size was determined based on Stage 1. For Stage 2, no hypothesis testing was underlying the sample size.

Randomisation and blinding (masking)

All participants were centrally assigned to randomised study intervention using an interactive randomisation technology (IRT) at Visit 1 within Stage 1 of the study. Stage 2 of Study B1971057 was an open-label study.

Assessor's comment

Randomisation was not considered relevant for the current procedure. Both group 2 and 4 received identical interventions of Trumenba.

Stage 2 was open-label. It is designed to evaluate the duration of the immune response after the second dose of the primary vaccination sequence and safety and immunogenicity of a booster dose, both of which are not considered to be impacted by the open-label design of the study as participant already had received multiple doses of Trumenba.

Statistical Methods

The MenB immune response induced by 2 doses of bivalent rLP2086 was described by compiling results for Groups 2 and 4.

For the calculation of GMTs, hSBA results below LLOQ were set as ½ of LLOQ. Two-sided 95% confidence intervals (CIs) were provided for all proportions and GMTs.

Exact 2-sided 95% CIs were compiled using the Clopper-Pearson method for any proportions of subjects with hSBA titers ≥ cutoff or LCI criteria.

Geometric means were obtained by log transformation of titers, averaging the transformed values, then exponentiating the results. Ninety-five percent CIs were also obtained for the geometric means. The CIs were calculated in the log scale with reference to the appropriate t-distribution. Then the lower and upper limits were exponentiated.

Analysis sets

The definition of the different analysis sets is presented in Table 3.

Table 3. Analysis population description

Population	Description
Stage 2 mITT	The mITT population for Stage 2 is defined as all subjects who signed the ICD at Visit 7 and who had at least 1 valid and determinate primary strain MenB or MenA/C/W/Y assay result available in Stage 2. The mITT population was analyzed according to the investigational product to which subjects were randomized. The Stage 2 mITT population was the analysis population for assessing the secondary immunogenicity endpoint of antibody persistence.
Booster Evaluable	The booster evaluable immunogenicity population included subjects who were eligible for the study (ie, met all Stage 1 eligibility criteria as well as continually meeting Stage 2 eligibility criteria), received a booster dose as intended (the same vaccine as they received in Stage 1), had blood drawn for assay testing within the required time frame at Month 55 (Visit 11), and had a valid and determinate MenB or MenA/C/W/Y assay result after the booster dose, as well as no major protocol violations as determined by the sponsor's global medical monitor.
Booster Vaccination Safety	The booster vaccination safety population included all subjects who received the booster dose of investigational product (MenABCWY or bivalent rLP2086) at Visit 10, and for whom safety information from Visit 10 up to and including Visit 11 was available.
Booster safety population	The booster safety population included all subjects who receive the booster dose of investigational product at Visit 10, and for whom safety information from Visit 10 up to and including Visit 12 is available.

Missing data

If 10% or more of the subjects in any strata had missing hSBA data for the 4 primary MenB strains, a sensitivity analysis using mixed-effects model with repeated measures (MMRM) for Groups 2 and 4 would be applied for the primary MenB strains (GMT). The MMRM used maximum likelihood estimation under the assumption that the missingness was at random (MAR). To account for the intrasubject correlation among the repeated measures, an unstructured covariance matrix would be used. In case the model did not converge, further covariance structures would be explored (i.e., first-order autoregressive, compound symmetry).

Log (hSBA) = race + sex + geographic location (US; ex-US) + age at randomisation + visit. The intercept would be set as random effect.

Assessor's comment

No hypothesis testing was performed for Stage 2. The results were presented descriptively.

Results

Participant flow

Participants were randomly selected at the end of Stage 1 to be contacted to be enrolled in Stage 2. A summary of the disposition of all randomised participants is presented in Table 4.

Table 4. Disposition of participants

	Group 2 (ACWY-naïve) (N[a]=537) n[b] (%)	Group 4 (ACWY-experienced) (N[a]=529) n[b] (%)	Groups 2+4 combined (N[a])=1066 N[b] (%)
Randomized[c]	544	522	1066
Randomized (actual ACWY history)	537	529	1066
Eligible for Stage 2[d]	458 (85.3)	458 (86.6)	916 (95.9)
Agreed to proceed to Stage 2	65 (12.1)	73 (13.8)	138 (12.9)
Entered Stage 2[e]	65	73	138

Completed Visit 7 (antibody persistence blood draw 1)	63 (96.9)	23 (31.5)	86 (62.3)
Completed Visit 8 (antibody persistence blood draw 2)	61 (93.8)	71 (97.3)	132 (95.7)
Completed Visit 9 (antibody persistence blood draw 3)	55 (94.6)	68 (93.2)	123 (89.1)
Withdrawn before booster vaccination	24 (36.9)	15 (20.5)	39 (28.3)
Lost to follow-up	7 (10.8)	6 (8.2)	13 (9.4)
No longer meets eligibility criteria	5 (7.7)	0	5 (3.6)
Other	1 (1.5)	3 (4.1)	4 (2.9)
Physician decision	1 (1.5)	0	1 (0.7)
Pregnancy	1 (1.5)	0	1 (0.7)
Withdrawal by parent/legal guardian	2 (3.1)	0	2(1.4)
Withdrawal by participant	7 (10.8)	6 (8.2)	13 (9.4)
Received booster vaccination	40	58	98
Completed Visit 11	38 (95.0)	58 (100.0)	96 (98.0)
Completed Visit 12	38 (95.0)	58 (100.0)	96 (98.0)
Withdrawn during safety follow-up	2 (5.0)	0	2 (2.0)
Lost to follow-up	1 (2.5)	0	1 (1.0)
Withdrawal by participant	1 (2.5)	0	1 (1.0)

Note: The vaccine group (as randomized), uses the actual ACWY history, which is based on prior receipt of a meningococcal group A, C, W, and Y vaccine.
Note: One participant was missing disposition records and did not receive the booster vaccination in Stage 2.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. "Randomized" refers to number of randomized participants for each group as per randomization schedule not adjusted for "actual ACWY history."
d. Participants that completed Visit 6 were randomly selected to participate in Stage 2. A back-up list was randomly generated to replace any primary participants that declined Stage 2 participation or could not be contacted.
e. Entered Stage 2 values is based on participant completion of Stage 2 informed consent. The values were used as the denominator for the percentage calculations for the Stage 2 section.

Assessor's comment

It was planned to enrol approximately 65 participants in both Group 2 and 4 in Stage 2.

The MAH was requested to explain why only 23 out of 73 participant (31.5%) of Group 4 completed Visit 7 (antibody persistence blood draw 1). The MAH provided more information regarding the collected data at Visit 7 and clarified that the decision to enrol ACWY experienced participants (Groups 3 and 4) into Stage 2 was made at a later stage (protocol amendment 2). Therefore, most of these participants were past the window for Visit 7, the 12-month blood draw before enrolling in Stage 2 and Visit 7 was not performed. In addition, the MAH was requested to discuss the impact of the missing data of these 50 participants on the month 12 results, by comparing the data for the 2 groups of participants (with and without Visit 7) at baseline, 1 month after vaccination 2, 24 months after vaccination 2 and 48 months after vaccination 2. Upon request, the MAH compared the immune responses for MenB between participants who did or did not participate at Visit 7. These seemed comparable.

The main reasons for withdrawal during the persistence follow-up period (Visit 6 through 10) were lost to follow-up and withdrawal by participant in both Groups.

Almost all participants who received the booster vaccination completed the safety follow-up until 6 months after vaccination. Again the reasons for withdrawal were lost to follow-up and withdrawal by participant.

None of the withdrawals during Stage 2 were linked to AEs.

Recruitment

The first subject was enrolled on 24 April 2017. The last participant last visit occurred on 25 October 2022 and database was released on 25 January 2023.

The study was conducted at 68 sites in Stage 1 with 39 of those sites participating in Stage 2 in the following countries: United States, Czech Republic, Finland, and Poland.

Baseline data

Demographic characteristics were generally similar across groups (see Table 5). Overall, most participants were white (93.8%) with 5.2% Black or African American participants, and 1.0% Asian participants. There were 4.2% Hispanic/Latino participants. The median age at the time of booster vaccination was 19.0 years, and 42.7% of participants were male.

Table 5. Demographic Characteristics During Booster Vaccination Phase – Booster Safety Population

	Group 2 (ACWY-naïve) (N[a]=40) n[b] (%)	Group 4 (ACWY-experienced) (N[a]=56) n[b] (%)	Groups 2+4 combined (N[a])=1066 N[b] (%)
Sex			
Male	14 (35.0)	27 (48.2)	41 (42.7)
Female	26 (65.0)	29 (51.8)	55 (57.3)
Race			
White	37 (92.5)	53 (94.6)	90 (93.8)
Black or African American	3 (7.5)	2 (3.6)	5 (5.2)
Asian	0	1 (1.8)	1 (1.0)
Ethnicity			
Hispanic/Latino	3 (7.5)	1 (1.8)	4 (4.2)
Non-Hispanic/non-Latino	37 (92.5)	55 (98.2)	92 (95.8)
Geographical location			
US	35 (87.5)	21 (37.5)	56 (58.3)
Ex-US	5 (12.5)	35 (62.5)	40 (41.7)
Age at booter vaccination (years)			
Mean (SD)	18.5 (5.51)	21.1 (4.11)	20.0 (4.89)
Median	15.5	20.0	19.0
Min, max	(14.0, 30.0)	(15.0, 30.0)	(14.0, 30.0)

Abbreviation: Ex-US = global, not including the United States.
Note: Two (2) participants in Group 4 who received MenABCWY at the booster vaccination instead of bivalent rLP2086 + MenACWY-CRM (Stage 1) were excluded from this table.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = number of participants in the specified category.

Assessor's comment

Due to small numbers substantial differences in baseline characteristics were observed between Group 2 and 4. Differences in sex and age could potentially influence the results relating to MenB assessments in the 2 groups. However, for the majority of endpoints the combined group will be the main focus.

Numbers analysed

Of the 138 subjects who entered Stage 2 in group 2 and 4, 98 subjects received the booster vaccination and 88 (89.8%) were included in the booster evaluable immunogenicity population. The persistence safety population included all 138 participants who entered Stage 2. The booster safety population

included the 96 participants who received the correct booster vaccine (i.e., 2 participants in Group 4 were excluded as they received MenABCWY vaccine as a booster).

Table 6. Immunogenicity Populations – Stage 2

	Group 2 (ACWY-naïve) n[a] (%)	Group 4 (ACWY-experienced) n[a] (%)	Groups 2+4 combined n[a] (%)
Randomized[b]	537	529	1066
Entered Stage 2[c]	65	73	138
Stage 2 mITT population	64 (98.5)	73 (100.0)	137 (99.3)
Excluded from Stage 2 mITT population	1 (1.5)	0	1 (0.7)
Received booster vaccination[d]	40	58	98
Booster evaluable immunogenicity population	37 (92.5)	51 (87.9)	88 (89.8)
Excluded from booster evaluable immunogenicity population	3 (7.5)	7 (12.1)	10 (10.2)
Reason for exclusion			
Did not continually meet Stage 1 or 2 eligibility criteria	1 (2.5)	2 (3.4)	3 (3.1)
Did not receive a booster dose as intended (ie same vaccine as during Stage 1)	0	2 (3.4)	2 (2.0)
Did not have blood draw or was out of window for assay testing at Visit 11 (month 55)	2 (5.0)	3 (5.2)	5 (5.1)
Did not have valid and determinate assay results after booster dose	2 (5.0)	2 (3.4)	4 (4.1)
Had major protocol violation	0	2 (3.4)	2 (2.0)

MenB = Neisseria meningitidis serogroup B.
a. n = Number of participants with the specified characteristic.
b. The values in this row were used as the denominators for the percentage calculations.
c. "Entered Stage 2" values are based on participant completion of Stage 2 informed consent period. The values from this row were used as the denominators for the percentage calculations of the mITT population.
d. The values were used as the denominator for the percentage calculations for the booster section.

Assessor's comment

The main reasons for exclusion from booster evaluable population were comparable between the 2 groups and included "did not have blood draw or out of window for assay at Visit 11" and "did not have a valid and determinate assay result after booster dose".

Efficacy results

Persistence results

The proportion of bivalent rLP2086 + MenACWY-CRM group recipients with protective MenB hSBA titers ≥ LLOQ declined during the first 12 months following the final dose of the primary vaccination and remained generally stable but higher than baseline through 48 months across the 4 primary MenB test strains, see Table 7.

Table 7. Participants With hSBA Titers ≥ LLOQ for Primary MenB Strains – Bivalent rLP2086 (Groups 2+4 Combined) – Persistence Analysis – Stage 2 mITT Population

	Groups 2+4 combined (bivalent rLP2086+MenACWY-CRM)			
	N[a]	nb	%	(95% CIc)
PMB80 (A22)				
Before Vaccination 1	133	30	22.6	(15.8, 30.6)
1 Month after Vaccination 2	137	127	92.7	(87.0, 96.4)
12 Months after Vaccination 2	83	22	26.5	(17.4, 37.3)
24 Months after Vaccination 2	128	37	28.9	(21.2, 37.6)
36 Months after Vaccination 2	116	30	25.9	(18.2, 34.8)
48 Months after Vaccination 2	94	30	31.9	(22.7, 42.3)

PMB2001 (A56)				
Before Vaccination 1	132	13	9.8	(5.3, 16.3)
1 Month after Vaccination 2	136	133	97.8	(93.7, 99.5)
12 Months after Vaccination 2	84	27	32.1	(22.4, 43.2)
24 Months after Vaccination 2	131	44	33.6	(25.6, 42.4)
36 Months after Vaccination 2	118	40	33.9	(25.4, 43.2)
48 Months after Vaccination 2	98	29	29.6	(20.8, 39.7)
PMB2948 (B24)				
Before Vaccination 1	137	10	7.3	(3.6, 13.0)
1 Month after Vaccination 2	135	108	80.0	(72.3, 86.4)
12 Months after Vaccination 2	85	24	28.2	(19.0, 39.0)
24 Months after Vaccination 2	131	36	27.5	(20.0, 36.0)
36 Months after Vaccination 2	120	34	28.3	(20.5, 37.3)
48 Months after Vaccination 2	98	26	26.5	(18.1, 36.4)
PMB2707 (B44)				
Before Vaccination 1	136	4	2.9	(0.8, 7.4)
1 Month after Vaccination 2	135	130	96.3	(91.6, 98.8)
12 Months after Vaccination 2	85	13	15.3	(8.4, 24.7)
24 Months after Vaccination 2	132	24	18.2	(12.0, 25.8)
36 Months after Vaccination 2	121	24	19.8	(13.1, 28.1)
48 Months after Vaccination 2	99	16	16.2	(9.5, 24.9)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; MenB = Neisseria meningitidis serogroup B.
Note: LLOQ = 1:16 for A22; 1:8 for A56, B24, and B44.
a. N = number of participants with valid and determinate hSBA titers for the given strain.
b. n = Number of participants with observed hSBA titer ⩾ LLOQ for the given strain at the given time point.
c. Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.

Booster analysis

At 1 month after a booster dose administered 48 months after Vaccination 2, the proportions of bivalent rLP2086 + MenACWY-CRM recipients achieving hSBA titers ≥ LLOQ for the 4 primary MenB test strains were higher than those at 1 month after Vaccination 2, see Table 8.

Table 8. Participants With hSBA Titers ≥ LLOQ for Primary MenB Strains – Bivalent rLP2086 (Groups 2+4 Combined) – Booster Evaluable Immunogenicity Population

	Groups 2+4 combined (bivalent rLP2086+MenACWY-CRM)			
	N[a]	nb	%	(95% CIc)
PMB80 (A22)				
1 Month after Vaccination 2	88	82	93.2	(85.7, 97.5)
Before booster vaccination	83	26	31.3	(21.6, 42.4)
1 month after booster vaccination	81	76	93.8	(86.2, 98.0)
PMB2001 (A56)				
1 Month after Vaccination 2	87	84	96.6	(90.3, 99.3)
Before booster vaccination	86	25	29.1	(19.8, 39.9)
1 month after booster vaccination	86	85	98.8	(93.7, 100.0)
PMB2948 (B24)				
1 Month after Vaccination 2	87	68	78.2	(68.0, 86.3)
Before booster vaccination	86	21	24.4	(15.8, 34.9)
1 month after booster vaccination	84	80	95.2	(88.3, 98.7)
PMB2707 (B44)				
1 Month after Vaccination 2	86	82	95.3	(88.5, 98.7)
Before booster vaccination	87	14	16.1	(9.1, 25.5)
1 month after booster vaccination	86	85	98.8	(93.7, 100.0)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; MenB = Neisseria meningitidis serogroup B.
Note: LLOQ = 1:16 for A22; 1:8 for A56, B24, and B44.
a. N = number of participants with valid and determinate hSBA titers for the given strain.
b. n = Number of participants with observed hSBA titer ⩾ LLOQ for the given strain at the given time point.
c. Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.

At 1 month after a booster dose administered 48 months after Vaccination 2, a substantial rise over pre-booster hSBA GMTs was demonstrated for the 4 primary Men B test strains.

	Groups 2+4 combined (bivalent rLP2086+MenACWY-CRM)		
	N[a]	GMT[b]	(95% CI[c])
PMB80 (A22)			
1 Month after Vaccination 2	88	43.5	(36.2, 52.3)
Before booster vaccination	83	11.6	(10.1, 13.4)
1 month after booster vaccination	81	74.7	(60.3, 92.5)
PMB2001 (A56)			
1 Month after Vaccination 2	87	123.0	(97.5, 155.2)
Before booster vaccination	86	6.6	(5.4, 8.0)
1 month after booster vaccination	86	223.2	(172.0, 289.7)
PMB2948 (B24)			
1 Month after Vaccination 2	87	16.9	(13.5, 21.2)
Before booster vaccination	86	5.9	(5.0, 7.1)
1 month after booster vaccination	84	40.7	(33.1, 49.9)
PMB2707 (B44)			
1 Month after Vaccination 2	86	34.1	(27.5, 42.4)
Before booster vaccination	87	5.0	(4.4, 5.7)
1 month after booster vaccination	86	66.1	(53.3, 81.9)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; MenB = Neisseria meningitidis serogroup B.
Note: LLOQ = 1:16 for A22; 1:8 for A56, B24, and B44.
a. N = number of participants with valid and determinate hSBA titers for the given strain.
b. GMTs were calculated using all participants with valid and determinate hSBA titers at the given time point..
c. CIs are back transformations of confidence levels based on the Student t distribution for the mean logarithm of the hSBA titers.

Assessor's comment

From month 24 after vaccination 2 through to month 48 after vaccination 2 no clear decrease in the proportion of participants achieving hSBA titers ≥LLOQ was observed. From month 24 through 48 after vaccination the proportion of participants achieving hSBA titers ≥LLOQ ranged from 25.9-31.9% for A22, 29.6-33.9% for A56, from 26.5-28.3% for B24 and 16.2-19.8% for B44. As only 23 out of 73 participant (31.5%) of Group 4 completed Visit 7 (antibody persistence blood draw 1), no clear conclusions can be drawn on the month 12 data. However, from a persistence perspective, it can agreed that in at least for 3 out of 4 MenB strains the proportion of participants achieving hSBA titers ≥LLOQ was higher than baseline up to month 48 after vaccination 2. For PBM80 (A22), from month 24 after vaccination 2, the proportion of participants with hSBA titers ≥LLOQ was considered comparable to baseline as 95% CI clearly overlap.

The results of the persistence data obtained from the 138 participants who entered Stage 2 are in general in line with previous results on persistence based on the results for study 1012, which are already included in the SmPC. No clear trend in reduction in proportion of participants achieving hSBA titers ≥LLOQ was observed from month 12 to month 48 during study 1012. The proportion of participants achieving hSBA titers ≥LLOQ at month 48 was slightly lower in the current study (1057) compared to study 1012. This might be due to differences in the study population included in both studies.

At 1 month after booster vaccination, the proportion of participants achieving hSBA titers ≥LLOQ was >93%. The hSBA GMT levels for the 4 primary strains were substantially higher 1 month after the booster dose compared to 1month after the primary vaccination. This indicates that a strong anamnestic response was induced by the booster dose, as hSBA GMTs were higher 1 month after the booster vaccination compared to 1 month after the primary series.

The proportion of participants achieving hSBA titers ≥LLOQ after the booster vaccination was comparable between the current study and study 1012, with the proportion of participants achieving hSBA titers ≥LLOQ being >93% in both studies for all strains. However, it is noteworthy that the hSBA GMT titers were substantially lower in the current study compared to study 1012.

Upon request the MAH indicated that comparing GMT results measured in different studies using bioassays should be avoided or done with caution. In addition, the MAH argued point estimates for GMTs in Study 1971057 although lower than in previous studies, are well above protective levels and higher than after the primary series.

Safety results

The B1971057 Stage 2 analysis was composed of safety data from 6 months following completion of the primary vaccination series (after Visit 5) through 6 months after booster vaccination.

Persistence Phase

In total, 353 participants agreed to enter Stage 2, 215 in the MenABCWY group and 138 in the bivalent rLP2086+MenACWY group. Of these participants, 253 (71.7%), 332 (94.1%), and 317 (89.8%) completed antibody persistence blood draws at 12, 24, and 36 months, respectively, after Vaccination 2 and 242 (68.6%) completed the 48-month persistence blood draw after Vaccination 2.

Persistence Phase (interval from 6 months following completion of the primary vaccination series [after Visit 5] and concludes prior to booster vaccination [before Visit 10]). During this phase, the following events were reportable: research related injuries and nonserious AEs that occurred within 48 hours of the persistence blood draws on visit 7 through 9. During the interval of time after Visit 5 until Visit 10, reporting of SAEs was not required unless the event was considered related to investigational product (IP) or at the discretion of the investigator.

There were a total of 9 AEs reported by 8 participants in the MenABCWY group (1 severe, 6 moderate and 2 mild) and 5 AEs reported by 5 participants in the bivalent rLP2086+ MenACWY-CRM group (2 severe, 2 moderate and 1 mild). None of the AEs were assessed as related to IP by the investigator.

Of these 14 AEs reported during the persistence phase:

- 2 AEs that were judged by the investigator to meet protocol exclusionary criteria led to the withdrawal of 2 participants from the study after Visit 5 (6 months after Vaccination 2). The 2 AEs were: severe major depressive disorder reported 1192 days after Vaccination 2 in 1 participant in the bivalent rLP2086 + MenACWY-CRM group and epilepsy reported 457 days after vaccination 2 in 1 participant in the MenABCWY group. Both events were reported during a non-active collection period (after Visit 5 to before Visit 10 [booster vaccination]).
- Major adverse events (MAEs) were reported by 3 participants. One participant in the bivalent rLP2086 + MenACWY-CRM group reported an MAE and an NDCMC of autoimmune thyroiditis. The event was reported 233 days after Vaccination 2. Two participants in the MenABCWY group reported MAEs of hypothyroidism (648 days after vaccination 2) and vulvovaginal candidiasis (1394 days after vaccination 2). The event of hypothyroidism was confirmed by laboratory testing to be of non-autoimmune origin.
- In total 6 SAEs were reported:
    - In the bivalent rLP2086 + MenACWY CRM group, 3 SAEs were reported by 3 subjects: spontaneous abortion that occurred 678 days after Vaccination 2 reported in 1 participant; severe viral meningitis that was reported 238 days after Vaccination 2 in a second participant; and severe major depressive disorder that was reported 1192 days after Vaccination 2 in a third participant.
    - In the MenABCWY group, 3 SAEs were reported by 3 subjects: epilepsy (sponsor confirmed neuroinflammatory condition) that was reported 457 days after Vaccination

2 in 1 participant; spontaneous abortion that occurred 1295 days after Vaccination 2 in a second participant; and severe spontaneous abortion that occurred 1201 days after Vaccination 2 in a third participant.

- There were no deaths reported.
- There were no AEs or research related injuries reported within 48 hours after the blood draws at Visit 7 through Visit 9.

Assessor's comment

In total 14 AEs were reported from 6 months after the primary series and before booster vaccination. Of these AEs 2 led to exclusion of participants: diagnosis of severe major depressive disorder and epilepsy. Based on the exclusion criteria of the study it can be agreed that the participants who developed epilepsy and major depressive disorder were excluded from the study. Both events were considered not related the investigational product which can be agreed. Of the 14 AEs, 6 were considered SAEs. The SAEs can be considered not possibly related to vaccination, as there is no clear time relationship to vaccination nor a biological plausible mechanism to explain these SAEs of abortion (n=3), epilepsy (n=1), major depression (n=1), and viral meningitis (n=1).

The MAH was asked to comment on the fact that the listings report vomiting and dizziness in one participant and syncope due to blood draw in one participant which were caused by blood draw according to the investigator. However, no research related injuries or AEs within 48 hours after blood draw were reported. Otherwise, it is not understood why these AEs that were reported as they were all mild to moderate in intensity, were not considered SAEs, MAEs, NDCMCs or immunological AEs. The MAH provided more information upon request regarding the cases of vomiting/dizziness and syncope observed that were caused by blood draw according to the investigator. Based on the provided narratives, it is in line with the protocol that these are reported as AE, but not reported as Research Related Injuries (RRI).

Booster vaccination phase (including follow-up)

Booster Vaccination Phase (interval from booster vaccination [Visit 10] through approximately 1 month after booster vaccination [Visit 11]). During this phase, the following events were reportable:

- Reactogenicity: local reactions, systemic events and use of antipyretic medication were to be recorded in the e-diary from the day of booster vaccination (Day 1) to Day 7 after booster vaccination.
- Immediate AEs: reported within 30 minutes after booster vaccination during the booster vaccination phase.
- AEs, SAEs, MAEs, NDCMCs, and days of missed school or work because of an AE during the booster vaccination phase (from booster vaccination [Visit 10] through approximately 1 month after booster vaccination [Visit 11]).

Exposure

In total 242 participants received a booster vaccination. The booster safety population consisted of 240 participants, including 144 MenABCWY recipients and 96 bivalent rLP2086 + MenACWY-CRM recipients.

- Due to a programming error which led to an IRT dispensing error, two participants received the incorrect IP at Visit 10 (Booster) and were administered MenABCWY instead of bivalent rLP2086 + MenACWY-CRM (as per their assignment in Stage 1).

Assessor's comment

In total 242 participants received a booster vaccination containing a form of Trumenba. Of these participants 2 received MenABCWY instead of rLP2086 + MenACWY-CRM. These 2 participants were excluded from the safety analysis. The MAH was asked to present the all relevant safety information on these participants, including at least any AEs considered related to the vaccine, SAEs, MAEs and NDCMCs experienced during the booster vaccination phase and follow-up until 6 months. Safety information for two participants who received a mixed regimen of rLP2086+MenACWY and MenABCWY was provided by the MAH upon request. Both participants experienced AEs, however these were considered unrelated to the investigational products.

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

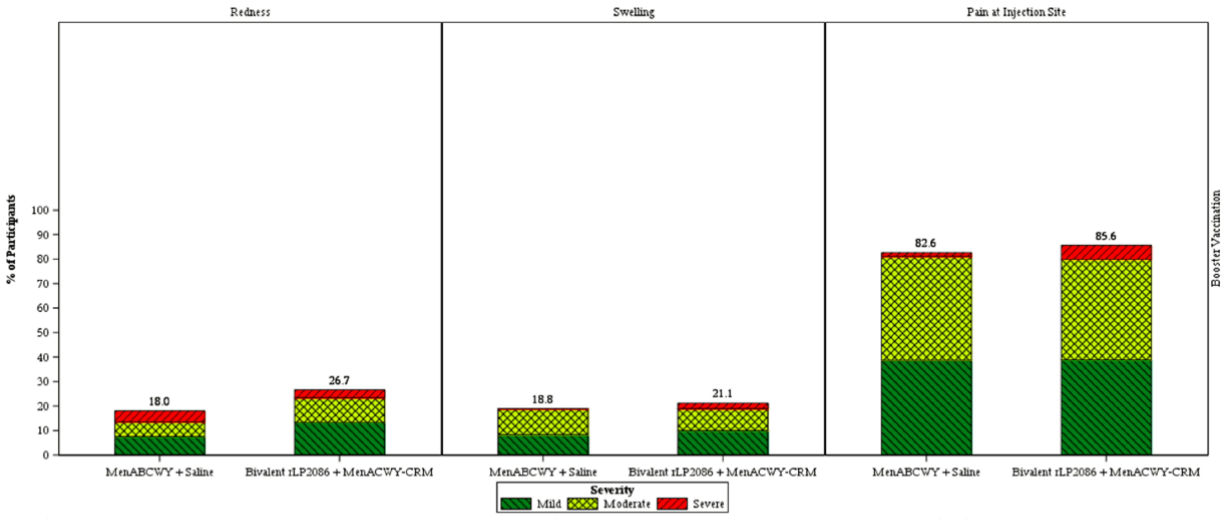
Local reactions

Local reactions (pain, swelling, and redness at the injection site) within 7 days after booster vaccination were reported in a similar percentage of MenABCWY participants (Groups 1+3 combined) and bivalent rLP2086 + MenACWY-CRM participants (Groups 2+4 combined). Pain at the injection site was the most commonly reported local reaction, see Figure 1. Most local reactions were mild or moderate in severity after the booster dose. There were no withdrawals due to local reactions in either vaccine group.

Large local reactions of redness (>21 caliper units [>10.5 cm]) were reported in 6 participants in the MenABCWY group and 2 participants in the bivalent rLP2086 + MenACWY-CRM group. There was one participant with a large local reaction of swelling (>21 caliper units) in the bivalent rLP2086 + MenACWY-CRM group.

The median onset for most local reactions was Day 1.0 to Day 2.0 after booster vaccination, and the majority of events resolved within a median duration of 2.0 to 3.0 days in both vaccine groups.

Figure 1. Local Reactions, by Maximum Severity, Within 7 Days After Booster Vaccination, MenABCWY and Bivalent rLP2086 – Booster Safety Population



In Study B1971057, Stage 2, MenABCWY Groups: Booster vaccination = MenABCWY. Bivalent rLP2086 + MenACWY-CRM Groups: Booster vaccination = bivalent rLP2086 + MenACWY-CRM.
Note: One report of mild injection site pain for 1 participant was queried and confirmed by the investigational site to have been entered in error. This data is considered missing in the database and reported as such. Number above each bar denotes percentage of participants reporting the events with any severity.
Note: Two (2) participants in Group 4 who received MenABCWY at the booster vaccination instead of bivalent rLP2086 + MenACWY-CRM (Stage 1) were excluded from this table.
Note: Local reactions are summarized for the MenABCWY or bivalent rLP2086 injection site for the left arm only. 5 participants received bivalent rLP2086 and 4 participants received MenABCWY in the right arm were excluded. The number of participants with known values in the interval is used as the denominator for percentages for each group. For redness and swelling, mild is >2.0 to 5.0 cm, moderate is >5.0 to 10.0 cm, severe is >10.0 cm. For pain at the injection site, mild = does not interfere with activity, moderate = interferes with activity, severe = prevents daily activity.

Systemic reactions

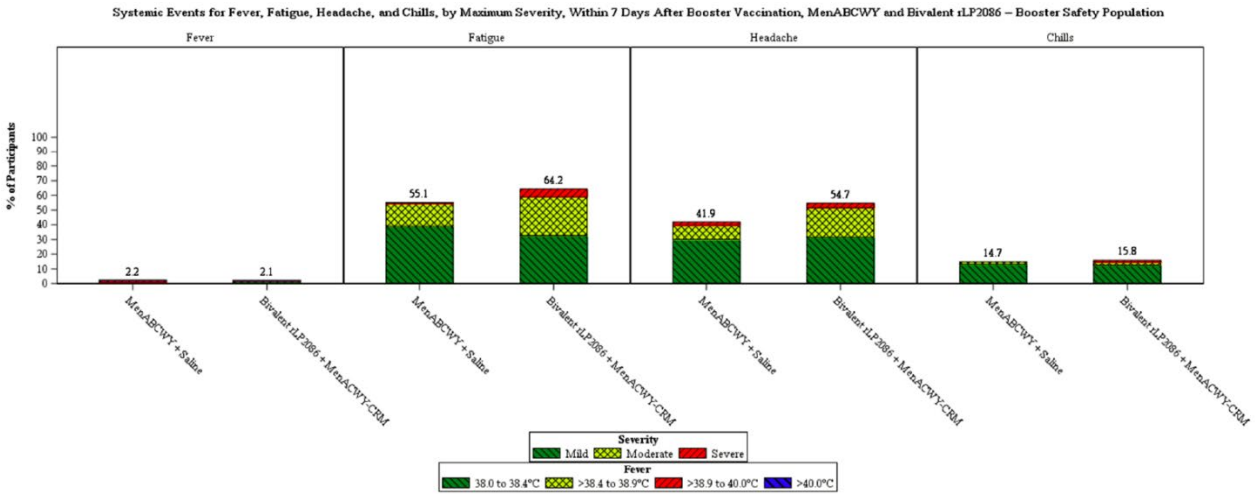
Systemic events within 7 days after booster vaccination were reported in a similar percentage of MenABCWY participants (Groups 1+3 combined) and bivalent rLP2086 + MenACWY-CRM participants (Groups 2+4 combined). Fatigue and headache were the most commonly reported systemic events.

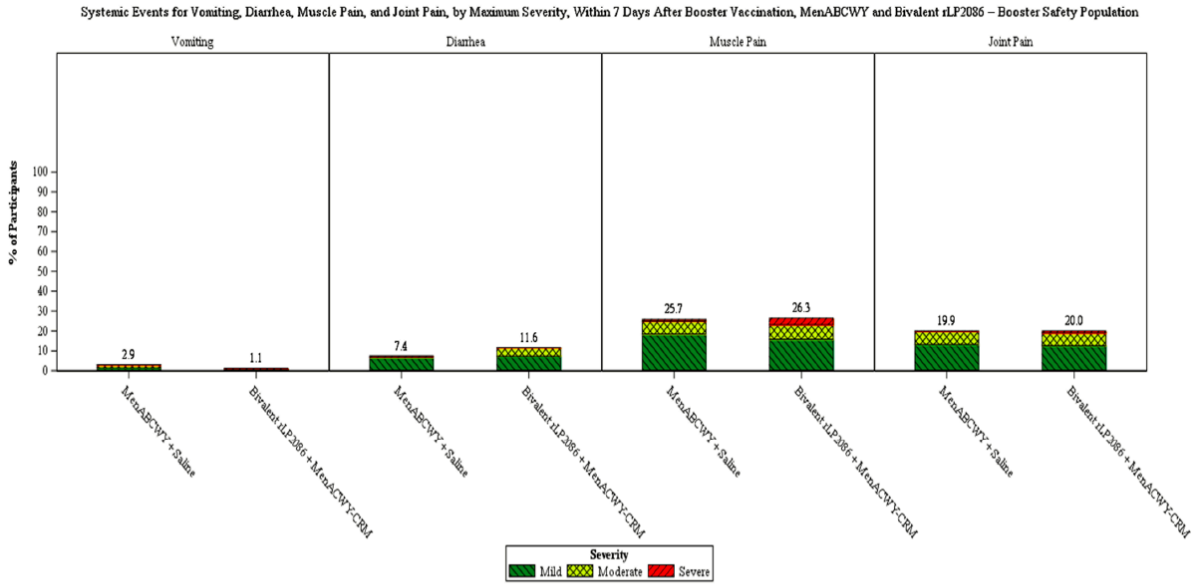
Most systemic events were mild or moderate in severity after the booster dose. There were no withdrawals due to systemic events in either vaccine group.

The median onset for most systemic events was Day 2.0 after booster vaccination however, the onset ranged from 1.0 to 4.0 days for some systemic events. The majority of events resolved within a median duration of 1.0 to 2.0 days in both vaccine groups.

Use of antipyretic/pain medication after the booster dose was reported by 14.7% of participants in both the MenABCWY and bivalent rLP2086+MenACWY-CRM groups.

Figure 2. Systemic Events for Fever, Fatigue, Headache, Chills, Vomiting, Diarrhoea, Muscle Pain, and Joint Pain, by Maximum Severity, Within 7 Days After Booster Vaccination, MenABCWY and Bivalent rLP2086 – Booster Safety Population





In Study B1971057, Stage 2, MenABCWY Groups: Booster Vaccination = MenABCWY. Bivalent rLP2086 + MenACWY-CRM Groups: Booster Vaccination = bivalent rLP2086 + MenACWY-CRM.
Note: Two (2) participants in Group 4 who received MenABCWY at the booster vaccination instead of bivalent rLP2086 + MenACWY-CRM (Stage 1) were excluded from this table.
Note: One report of mild headache for 1 participant and one report of mild joint pain for 1 participant were queried and confirmed by the investigational site to have been entered in error. These data are considered missing in the database and reported as such.
Number above each bar denotes percentage of participants reporting the events with any severity.
The number of participants with known values in the interval is used as the denominator for percentages for each group.

Assessor's comment

Trumenba is a reactogenic vaccine. A high proportion of subjects, >82%, reported local reactions following the booster vaccination, with pain at injection site being the most frequently reported. The majority of participants, >70%, reported any systemic event following the booster vaccination, with the most frequently reported systemic events being fatigue and headache. However, no subjects withdrew from the study based on the local or systemic reactions. The majority of events were mild to moderate.

These results are in line the reactogenicity profile of the primary series (see variation EMEA/H/C/004051/II/0032). The results are in line with what is known for the product.

Adverse Events

A summary of participants reporting at least 1 AE in the booster safety population during the booster vaccination phase (from booster vaccination through 1 month after booster vaccination) for MenABCWY (Groups 1+3 combined) and bivalent rLP2086 + MenACWY-CRM (Groups 2+4 combined) is presented in Table 9.

Table 9. Number (%) of Participants Reporting at Least 1 Adverse Event for Booster Analysis Interval – MenABCWY (Groups 1 and 3) and Bivalent rLP2086 (Groups 2 and 4) – Booster Safety Population

	Vaccine Group (as Administered [Actual ACWY History[a]])											
	Group 1 (MenABCWY + Saline)		Group 2 (Bivalent rLP2086 + MenACWY-CRM)		Group 3 (MenABCWY + Saline)		Group 4 (Bivalent rLP2086 + MenACWY-CRM)		Groups 1+3 Combined (MenABCWY + Saline)		Groups 2+4 Combined (Bivalent rLP2086 + MenACWY-CRM)	
Interval Adverse Event Type	N[b]	n[c] (%) (95% CI[d]) Number of Events[e]	N[b]	n[c] (%) (95% CI[d]) Number of Events[e]	N[b]	n[c] (%) (95% CI[d]) Number of Events[e]	N[b]	n[c] (%) (95% CI[d]) Number of Events[e]	N[b]	n[c] (%) (95% CI[d]) Number of Events[e]	N[b]	n[c] (%) (95% CI[d]) Number of Events[e]
During Booster vaccination phase[f]												
All AEs	67	9 (13.4) (6.3, 24.0) 15	40	4 (10.0) (2.8, 23.7) 5	77	8 (10.4) (4.6, 19.4) 9	56	10 (17.9) (8.9, 30.4) 11	144	17 (11.8) (7.0, 18.2) 24	96	14 (14.6) (8.2, 23.3) 16
Related	67	1 (1.5) (0.0, 8.0) 2	40	0 (0.0, 8.8) 0	77	1 (1.3) (0.0, 7.0) 1	56	0 (0.0, 6.4) 0	144	2 (1.4) (0.2, 4.9) 3	96	0 (0.0, 3.8) 0
Severe	67	0 (0.0, 5.4) 0	40	0 (0.0, 8.8) 0	77	0 (0.0, 4.7) 0	56	0 (0.0, 6.4) 0	144	0 (0.0, 2.5) 0	96	0 (0.0, 3.8) 0
All SAEs	67	0 (0.0, 5.4) 0	40	0 (0.0, 8.8) 0	77	0 (0.0, 4.7) 0	56	1 (1.8) (0.0, 9.6) 1	144	0 (0.0, 2.5) 0	96	1 (1.0) (0.0, 5.7) 1
Related	67	0 (0.0, 5.4) 0	40	0 (0.0, 8.8) 0	77	0 (0.0, 4.7) 0	56	0 (0.0, 6.4) 0	144	0 (0.0, 2.5) 0	96	0 (0.0, 3.8) 0
All MAEs	67	6 (9.0) (3.4, 18.5) 10	40	2 (5.0) (0.6, 16.9) 2	77	2 (2.6) (0.3, 9.1) 3	56	4 (7.1) (2.0, 17.3) 4	144	8 (5.6) (2.4, 10.7) 13	96	6 (6.3) (2.3, 13.1) 6
Related	67	0 (0.0, 5.4) 0	40	0 (0.0, 8.8) 0	77	1 (1.3) (0.0, 7.0) 1	56	0 (0.0, 6.4) 0	144	1 (0.7) (0.0, 3.8) 1	96	0 (0.0, 3.8) 0
All NDCMCs	67	0 (0.0, 5.4) 0	40	0 (0.0, 8.8) 0	77	0 (0.0, 4.7) 0	56	0 (0.0, 6.4) 0	144	0 (0.0, 2.5) 0	96	0 (0.0, 3.8) 0
Related	67	0 (0.0, 5.4) 0	40	0 (0.0, 8.8) 0	77	0 (0.0, 4.7) 0	56	0 (0.0, 6.4) 0	144	0 (0.0, 2.5) 0	96	0 (0.0, 3.8) 0

Abbreviations: MAE = medically attended adverse event; NDCMC = newly diagnosed chronic medical condition.
Note: Two (2) participants in Group 4 who received MenABCWY at the booster vaccination instead of bivalent rLP2086 + MenACWY-CRM (Stage 1) were excluded from this table.
a. "Actual ACWY history" is based on prior receipt of a meningococcal group A, C, W, and Y vaccine.
b. N = number of participants in the specified group. These values are the denominator for percentage calculations for the vaccines groups.
c. n = Number of participants reporting at least 1 occurrence of the event specified.
d. Exact 2-sided confidence interval (CI), based on the Clopper and Pearson method.
e. The total number of occurrences of the event specified. Participants can be represented more than once. Event counts are the sum of individual occurrences within that category.
f. The booster vaccination phase is from the booster vaccination (Visit 10) through 1 month after the booster vaccination (Visit 11).

During the booster vaccination phase, a similar percentage of participants reported at least 1 AE in the MenABCWY and the bivalent rLP2086 + MenACWY-CRM groups (17 [11.8%] and 14 [14.6%], respectively) (Table 9). The most commonly reported System Organ Class (SOC) was Infections and infestations, with the most frequently reported Preferred Term (PT) being COVID-19, followed by Investigations, with the most frequently reported PT being SARS-CoV-2 test positive.

The percentages of participants who reported related AEs were low and similar between the MenABCWY and the bivalent rLP2086 + MenACWY-CRM groups (2 [1.4%] and 0 [0.0%], respectively). There were 3 AEs considered by the investigator as related to study intervention, which were reactogenicity events: injection site pain, injection stie swelling and headache.

AEs reportable during the booster follow-up phase (1-month after booster vaccination through 6 months after the booster vaccination) only included SAEs, MAEs and NDCMCs. A summary of participants reporting at least 1 AE in the booster safety population during booster follow-up phase for MenABCWY (Groups 1+3 combined) and bivalent rLP1086 + MenACWY-CRM (Groups 2+4 combined) is presented in Table 10.

There were 144 participants in the MenABCWY group and 94 participants in the bivalent rLP2086 + MenACWY-CRM group included in the follow-up booster safety population

Table 10. Number (%) of Participants With at Least 1 Adverse Event Occurring During Booster Follow-up Phase – MenABCWY (Groups 1 and 3) and Bivalent rLP2086 (Groups 2 and 4) – Follow-up Booster Safety Population

	Vaccine Group (as Administered [Actual ACWY History[a]])											
	ACWY-Naive				ACWY-Experienced							
	Group 1 (MenABCWY + Saline)		Group 2 (Bivalent rLP2086 + MenACWY-CRM)		Group 3 (MenABCWY + Saline)		Group 4 (Bivalent rLP2086 + MenACWY-CRM)		Groups 1+3 Combined (MenABCWY + Saline)		Groups 2+4 Combined (Bivalent rLP2086 + MenACWY-CRM)	
Interval Adverse Event Type	N[b]	n[c] (%) (95% CI[d]) No. of Events[e]	N[b]	n[c] (%) (95% CI[d]) No. of Events[e]	N[b]	n[c] (%) (95% CI[d]) No. of Events[e]	N[b]	n[c] (%) (95% CI[d]) No. of Events[e]	N[b]	n[c] (%) (95% CI[d]) No. of Events[e]	N[b]	n[c] (%) (95% CI[d]) No. of Events[e]
During the Booster follow-up phase[f]												
All SAEs	67	0 (0.0, 5.4) 0	38	0 (0.0, 9.3) 0	77	2 (2.6) (0.3, 9.1) 3	56	0 (0.0, 6.4) 0	144	2 (1.4) (0.2, 4.9) 3	94	0 (0.0, 3.8) 0
Related	67	0 (0.0, 5.4) 0	38	0 (0.0, 9.3) 0	77	0 (0.0, 4.7) 0	56	0 (0.0, 6.4) 0	144	0 (0.0, 2.5) 0	94	0 (0.0, 3.8) 0
All MAEs	67	2 (3.0) (0.4, 10.4) 2	38	5 (13.2) (4.4, 28.1) 8	77	5 (6.5) (2.1, 14.5) 6	56	4 (7.1) (2.0, 17.3) 4	144	7 (4.9) (2.0, 9.8) 8	94	9 (9.6) (4.5, 17.4) 12
Related	67	0 (0.0, 5.4) 0	38	0 (0.0, 9.3) 0	77	0 (0.0, 4.7) 0	56	0 (0.0, 6.4) 0	144	0 (0.0, 2.5) 0	94	0 (0.0, 3.8) 0
All NDCMCs	67	0 (0.0, 5.4) 0	38	0 (0.0, 9.3) 0	77	2 (2.6) (0.3, 9.1) 2	56	0 (0.0, 6.4) 0	144	2 (1.4) (0.2, 4.9) 2	94	0 (0.0, 3.8) 0
Related	67	0 (0.0, 5.4) 0	38	0 (0.0, 9.3) 0	77	0 (0.0, 4.7) 0	56	0 (0.0, 6.4) 0	144	0 (0.0, 2.5) 0	94	0 (0.0, 3.8) 0

Abbreviations: MAE = medically attended adverse event; SAE = serious adverse event; NDCMC = newly diagnosed chronic medical condition.
Note: (MedDRA v25.1) coding dictionary applied.
Note: Two participants in Group 4 that received MenABCWY at the booster vaccination instead of bivalent rLP2086 + MenACWY-CRM (Stage 1) were excluded from this table.
a. "Actual ACWY history" is based on prior receipt of a meningococcal group A, C, W, and Y vaccine.
b. N = number of participants in the specified group. These values are the denominator for percentage calculations for the vaccines groups.
c. n = Number of participants reporting at least 1 occurrence of the event specified.
d. Exact 2-sided confidence interval (CI), based on the Clopper and Pearson method.
e. The total number of occurrences of the event specified. Participants can be represented more than once. Event counts are the sum of individual occurrences within that category.
f. The booster vaccination follow-up phase is defined as the time from 1 month after the booster vaccination (Visit 11) through 6 months after the booster vaccination (Visit 12).

Assessor's comment

After the booster, the percentage of participants experiencing an AE ranged from 10.0% to 17.9% in the 4 groups. In line with previous studies, the most commonly reported SOC was infections and infestations. AEs considered related to the investigational product were experienced by only 2 participants. These were all considered related to reactogenicity events.

Serious Adverse Events

During the booster vaccination phase, there was 1 pregnancy reported as an SAE in error in a participant in the bivalent rLP2086 + MenACWY-CRM group. Although pregnancies are reported to the

Pfizer Safety Database, pregnancy was not recorded as an AE in the clinical database, and this pregnancy was therefore reported as an AE in error.

During the booster follow-up phase 4 SAEs were reported by 3 participants; 3 SAEs were reported by 2 (1.4%) participants in the MenABCWY group with a left femur fracture in one participant and a right femur fracture and pulmonary embolism in another participant. One SAE of psychosis was reported for 1 participant in the mixed regimen group who received bivalent rLP2086 + MenACWY-CRM as primary series and MenABCWY incorrectly as booster. None of the reported SAEs were considered related to investigational product. A narrative for the SAE of psychosis was provided in the interim CSR dated 23 September 2022.

Assessor's comment

The percentage of participants experiencing SAEs is low during the booster phase and the follow-up of the booster phase, with only 3 out of 238 participants (1.3%) experiencing an SAE. None of the SAEs are considered related to the investigational product.

Death

No deaths were reported during Stage 2 in Study B1971057.

During Stage 1 of the study, one MenABCWY + saline recipient died 109 days after Vaccination 2 from a motor vehicle accident. The death was not considered by the investigator to be related to the investigational product.

Assessor's comment

The death now reported for Stage 1 was not previously reported. The death from motor vehicle accident is not considered related.

Discontinuation due to AE

There were 2 participants who were withdrawn from the study due to AEs that were considered unrelated to vaccine. There was one report of epilepsy in a participant in the MenABCWY group and one report of major depressive disorder in a participant in the bivalent rLP2086 + MenACWY-CRM group. Both events were reported during a non-active collection period (after Visit 5 to before Visit 10 [booster vaccination]). Both participants were withdrawn from the study because they no longer met the study inclusion criteria.

Assessor's comment

As stated above, the AEs of epilepsy and major depressive disorder, which were diagnosed during the persistence phase, are not considered related to the investigational product. Further it is agreed that these AEs would lead to exclusion based on inclusion/exclusion criteria.

2.3.3. Discussion on clinical aspects

The study provided limited data on persistence of immunogenicity. The number of participants who were included in Stage 2 represent approximately 13% of participants who entered Stage 1. The data on persistence was obtained from 138 participants included in Group 2 and 4 combined. Furthermore, persistence data was limited to the proportion of subjects with hSBA titers ≥LLOQ at several different time points after vaccination and hSBA GMT titers was not determined. In general the results on persistence are in line with the results obtained during study 1012 which are presented in the SmPC. During the current study, no clear decrease in the proportion of participants achieving hSBA titers ≥LLOQ was observed from month 24 after vaccination 2 through to month 48 after vaccination 2. For 3

out of 4 MenB strains the proportion of participants achieving hSBA titers ≥LLOQ was higher than baseline up to month 48 after vaccination 2. For PBM80 (A22), from month 24 after vaccination 2, the proportion of participants with hSBA titers ≥LLOQ was considered comparable to baseline as 95% CI clearly overlap. Since it was decided at a later stage (Protocol Amendment 2) to also include ACWY-experienced groups to evaluate immune persistence a large proportion of participants in Groups 3 and 4 did not complete Visit 7, no differences in immune responses at other time points was observed for those who did and did not complete Visit 7.

In total only 98 participants received a booster vaccination and only 88 were included in the booster evaluable immunogenicity population. The booster vaccination induced a strong anamnestic response with >93% of participants achieving hSBA titers ≥LLOQ for all strains. In addition, the hSBA GMT titers were higher 1 month after the booster vaccination compared to 1 month after the primary series. However, it is noteworthy that the hSBA GMT titers after the booster vaccination were substantially lower in the current study compared to study 1012.

During the persistence phase of the study, Visit 7 through Visit 9, in total 14 AEs were reported, of which 6 were SAEs. The majority of the reported SAEs can be considered not possibly related to vaccination, as there is no clear time relationship to vaccination nor a biological plausible mechanism to explain these SAEs of abortion (n=3), epilepsy (n=1), major depression (n=1), and viral meningitis (n=1).

After the booster dose, the reactogenicity profile of Trumenba was comparable to the reactogenicity profile after the primary series. Trumenba is a reactogenic vaccine, with the vast majority of participants experiencing a local or systemic AE. The majority of AEs were mild to moderate in intensity. No new safety signals were observed.

3. Request for supplementary information

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

1. The Applicant is requested to explain why only 23 out of 73 participant (31.5%) of Group 4 completed Visit 7 (antibody persistence blood draw 1). In addition, the MAH is requested to discuss the impact of the missing data of these 50 participants on the month 12 results, by comparing the data for the 2 groups of participants (with and without Visit 7) at baseline, 1 month after vaccination 2, 24 months after vaccination 2 and 48 months after vaccination 2.
2. It is noteworthy that the hSBA GMT titers after the booster vaccination were substantially lower in the current study compared to results from study 1012 as reported in the SmPC after the 2 dose regimen. The MAH is asked to explain this substantial difference in hSBA GMT titers, which might impact persistence of the response.
3. The MAH is asked to comment on the fact that listing 16.2.7.3 reports vomiting and dizziness in 1 participant and syncope due to blood draw in 1 participant which were caused by blood draw according to the investigator, however, no research related injuries or AEs within 48 hours after blood draw were reported.
4. The MAH is asked to present the all relevant safety information on the 2 participants who received a mixed regimen of rLP2086+MenACWY and MenABCWY, including at least any AEs considered related to the vaccine, SAEs, MAEs and NDCMCs experienced during the booster vaccination phase and follow-up until 6 months.

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

MAH responses to Request for supplementary information

Question 1

The Applicant is requested to explain why only 23 out of 73 participant (31.5%) of Group 4 completed Visit 7 (antibody persistence blood draw 1). In addition, the MAH is requested to discuss the impact of the missing data of these 50 participants on the month 12 results, by comparing the data for the 2 groups of participants (with and without Visit 7) at baseline, 1 month after vaccination 2, 24 months after vaccination 2 and 48 months after vaccination 2.

Applicant's Response

A decision was made, later in the course of Stage 1 of the study, to enroll ACWY experienced participants (eg, Group 4) into Stage 2 which resulted in most of these participants being outside the window for the Visit 7, 12-month blood draw.

The inclusion of ACWY-experienced participants in the immunopersistence and booster analyses of the study in addition to the ACWY-naïve participants, was requested by the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) and implemented with protocol amendment 2, dated 09 July 2019. Therefore, a greater number of ACWY-experienced participants were expected to be outside the window for Visit 7 than ACWY-naïve participants by the time protocol amendment dated 09 July 2019 was implemented. To address this issue, per the protocol amendment, omitting Visit 7 and beginning persistence blood draws at Visit 8 was allowed if participants were beyond window for Visit 7; as shown in Table 1, 69.9% of participants in Group 4 were beyond window to complete Visit 7. Note that 97.3% of Group 4 participants completed Visit 8.

Table 1. Percentage of participants in Group 4 who Enrolled into Stage 2 After the Protocol Specified Window to Complete Visit 7 (through 694 days after Visit 3) – Stage 2 ITT Population

	Vaccine Group (as Randomized [Actual ACWY History[a]]) ACWY-Experienced Group 4 (Bivalent rLP2086 + MenACWY-CRM) n[b] (%)
Entered Stage 2[c]	73
Enrolled into Stage 2 after window (336 to 694 Days After Visit 3)	51 (69.9)

Note: The vaccine group (as randomized), uses the actual ACWY history, which is based on prior receipt of a meningococcal group A, C, W, and Y vaccine.
a. "Actual ACWY history" is based on prior receipt of a meningococcal group A, C, W, and Y vaccine.
b. n = Number of participants with the specified characteristic.
c. Number of participants who enrolled in Stage 2.

Regarding the impact on the 12-month persistence data from the participants that missed the Visit 7 blood draw (12 months after Vaccination 2), please see Table 2, which compares data for baseline, 1-month, 24-months, and 48-months after Vaccination 2 between the participants that missed Visit 7 and those that completed Visit 7. Note that results are reported for Groups 2 and 4 combined, to be consistent with how immunopersistence data were reported in the CSR. Point estimates and associated CIs for the MenB strain responses for the timepoints indicate that the immune responses are comparable between the groups. It is therefore unlikely that those who missed the Visit 7 blood draw would have had lower 12-month titers than those who completed the Visit 7 blood draw. From this new analysis, there is no indication that immune responses at Visit 7 were overestimated.

Table 2. Number (%) of Participants With hSBA Titers ≥ LLOQ for Primary MenB Strains – Bivalent rLP2086 (Groups 2+4 Combined) – Persistence Analysis for Participants Who Did and Did Not Complete Visit 7 (Antibody Persistence Blood Draw 1) – Stage 2 mITT Population

	Vaccine Group (as Randomized [Actual ACWY History[a]]) Groups 2+4 Combined (Bivalent rLP2086 + MenACWY-CRM)											
	Participants Completed Visit 7 (Antibody Persistence Blood Draw 1)				Participants Not Completed Visit 7 (Antibody Persistence Blood Draw 1)				All Participants			
MenB Strain (Variant) Time Point	N[b]	n[c]	%	(95% CI[d])	N[b]	n[c]	%	(95% CI[d])	N[b]	n[c]	%	(95% CI[d])
PMB80 (A22)												
Before Vaccination 1	82	21	25.6	(16.6, 36.4)	51	9	17.6	(8.4, 30.9)	133	30	22.6	(15.8, 30.6)
1 Month after Vaccination 2	85	79	92.9	(85.3, 97.4)	52	48	92.3	(81.5, 97.9)	137	127	92.7	(87.0, 96.4)
24 Months after Vaccination 2	76	17	22.4	(13.6, 33.4)	52	20	38.5	(25.3, 53.0)	128	37	28.9	(21.2, 37.6)
48 Months after Vaccination 2	53	14	26.4	(15.3, 40.3)	41	16	39.0	(24.2, 55.5)	94	30	31.9	(22.7, 42.3)
PMB2001 (A56)												
Before Vaccination 1	81	10	12.3	(6.1, 21.5)	51	3	5.9	(1.2, 16.2)	132	13	9.8	(5.3, 16.3)
1 Month after Vaccination 2	84	84	100.0	(95.7, 100.0)	52	49	94.2	(84.1, 98.8)	136	133	97.8	(93.7, 99.5)
24 Months after Vaccination 2	79	28	35.4	(25.0, 47.0)	52	16	30.8	(18.7, 45.1)	131	44	33.6	(25.6, 42.4)
48 Months after Vaccination 2	53	16	30.2	(18.3, 44.3)	45	13	28.9	(16.4, 44.3)	98	29	29.6	(20.8, 39.7)
PMB2948 (B24)												
Before Vaccination 1	85	5	5.9	(1.9, 13.2)	52	5	9.6	(3.2, 21.0)	137	10	7.3	(3.6, 13.0)
1 Month after Vaccination 2	83	69	83.1	(73.3, 90.5)	52	39	75.0	(61.1, 86.0)	135	108	80.0	(72.3, 86.4)
24 Months after Vaccination 2	79	22	27.8	(18.3, 39.1)	52	14	26.9	(15.6, 41.0)	131	36	27.5	(20.0, 36.0)
48 Months after Vaccination 2	54	13	24.1	(13.5, 37.6)	44	13	29.5	(16.8, 45.2)	98	26	26.5	(18.1, 36.4)
PMB2707 (B44)												
Before Vaccination 1	85	3	3.5	(0.7, 10.0)	51	1	2.0	(0.0, 10.4)	136	4	2.9	(0.8, 7.4)

Table 2. Number (%) of Participants With hSBA Titers ≥ LLOQ for Primary MenB Strains – Bivalent rLP2086 (Groups 2+4 Combined) – Persistence Analysis for Participants Who Did and Did Not Complete Visit 7 (Antibody Persistence Blood Draw 1) – Stage 2 mITT Population

	Vaccine Group (as Randomized [Actual ACWY History[a]]) Groups 2+4 Combined (Bivalent rLP2086 + MenACWY-CRM)											
	Participants Completed Visit 7 (Antibody Persistence Blood Draw 1)				Participants Not Completed Visit 7 (Antibody Persistence Blood Draw 1)				All Participants			
MenB Strain (Variant) Time Point	N[b]	n[c]	%	(95% CI[d])	N[b]	n[c]	%	(95% CI[d])	N[b]	n[c]	%	(95% CI[d])
1 Month after Vaccination 2	84	83	98.8	(93.5, 100.0)	51	47	92.2	(81.1, 97.8)	135	130	96.3	(91.6, 98.8)
24 Months after Vaccination 2	80	15	18.8	(10.9, 29.0)	52	9	17.3	(8.2, 30.3)	132	24	18.2	(12.0, 25.8)
48 Months after Vaccination 2	55	10	18.2	(9.1, 30.9)	44	6	13.6	(5.2, 27.4)	99	16	16.2	(9.5, 24.9)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; MenB = *Neisseria meningitidis* serogroup B.
Note: LLOQ = 1:16 for A22; 1:8 for A56, B24, and B44.
a. "Actual ACWY history" is based on prior receipt of a meningococcal group A, C, W, and Y vaccine.
b. N = number of participants with valid and determinate hSBA titers for the given strain.
c. n = Number of participants with observed hSBA titer ≥ LLOQ for the given strain at the given time point.
d. Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.

Assessor's comment

The Applicant has clarified that the decision to enrol ACWY experienced participants (Groups 3 and 4) into Stage 2 was made at a later stage (protocol amendment 2). Therefore most of these participants were outside the window for Visit 7, the 12-month blood draw. Table 1 of the responses shows that of the 73 participants in group 3, 51 participants were enrolled after the Visit window. However, in Table 4 of the CSR, it is shown that 73 participants entered stage 2, with 23 participants completing Visit 7. The Applicant should clarify this discrepancy (**OC**).

The Applicant has provided the proportion of participants with hSBA titres above LLOQ stratified by participation at Visit 7 at baseline, 1 month after vaccination 2, 24 months after vaccination 2 and 48 months after vaccination 2 for the four primary MenB strains. It is agreed that based on point estimates and associated CIs the immune responses between participants who completed Visit 7 and who did not complete Visit 7 seem comparable for the MenB component.

This issue is **not resolved.**

Question 2

It is noteworthy that the hSBA GMT titers after the booster vaccination were substantially lower in the current study compared to results from study 1012 as reported in the SmPC after the 2 dose regimen. The MAH is asked to explain this substantial difference in hSBA GMT titers, which might impact persistence of the response

Applicant's Response

Pfizer acknowledges that the point estimates of the GMTs after booster vaccination in Study B1971057 were lower than the results reported after the 0- and 6- month dose schedule in the SmPC (primary series study [B1971012] and immunopersistence and booster study [B1971033]). Regarding this, Pfizer emphasizes 2 points:

1. Endeavoring to compare and interpret differences in GMT results of bioassays that were performed separately in different studies should be avoided or done with caution.

2. Despite lower point estimates after booster vaccination for the GMTs in Study B1971057, the MenB GMTs post-booster in Study B1971057 were still well above protective levels and were robust (A22=74.7; A56=223.2; B24=40.7; B44=66.1). These titers were higher than the responses after the primary series (indicative of an anamnestic booster response) for which the 48-month, pre-booster GMTs were still above the level considered a correlate of protection for MenB (≥1:4). For these reasons, the MAH does not believe there is a potential concern about the persistence of hSBA titers following a booster dose in Study B1971057.

Assessor's comment

The Applicant indicates that comparing GMT results measured in different studies using bioassays should be avoided or done with caution. In addition, the Applicant argues point estimates for GMTs in Study 1971057 although lower than in previous studies, are well above protective levels and higher than after the primary series.

A possible explanation for the observed differences in responses could also be a difference in the age groups included in the different studies. Participants of study B1971012 were 11-18 years at baseline, while in study B1971057 participants were 10-26 years of age at baseline.

Although there could be some influence of lower GMTs towards persistence of immune responses, given the high proportion of participants showing a anamnestic response after the booster dose the potential impact of the lower GMTs observed is considered limited, also since other immune factors might be (more) relevant for long-term protection.

This issue will not be further pursued.

Question 3

The MAH is asked to comment on the fact that listing 16.2.7.3 reports vomiting and dizziness in 1 participant and syncope due to blood draw in 1 participant which were caused by blood draw according to the investigator, however, no research related injuries or AEs within 48 hours after blood draw were reported.

Applicant's Response

The onset and resolution of AEs associated with blood draws for both Participants occurred and resolved on the same day as the blood draws without incident. No research related injuries (RRI) are listed in the CSR because per protocol, the 2 sites appropriately reported these events on an AE case report form as the events did not meet seriousness criteria for RRI.

All AEs occurring within 48 hours of persistence blood draws from Visit 7 through Visit 9 were to be reported. If an AE met specific criteria for a medically important RRI then it was to be reported as an RRI. A medically important RRI was defined per protocol as any untoward medical occurrence that: results in death; is life-threatening (immediate risk of death); requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions); or results in congenital anomaly/birth defect.

Assessor's comment

The Applicant has provided more information regarding the cases of vomiting/dizziness and syncope observed that were caused by blood draw according to the investigator. Based on the provided narratives it is agreed that in line with the protocol since the occurrence within 48 hours of blood draw these are reported as AE, but not reported as RRI.

This issue is considered resolved.

Question 4

The MAH is asked to present the all relevant safety information on the 2 participants who received a mixed regimen of rLP2086+MenACWY and MenABCWY, including at least any AEs considered related to the vaccine, SAEs, MAEs and NDCMCs experienced during the booster vaccination phase and follow-up until 6 months.

Applicant's Response

Both Participants and received the incorrect vaccine at the time of the booster dose and therefore received a mixed regimen of rLP2086+MenACWY and MenABCWY. One participant experienced 1 safety event - a mild, unrelated AE of upper respiratory tract infection that occurred during the booster vaccination phase (from booster vaccination through 1-month post-booster vaccination). The second participant, with a past medical history of insomnia, dysthymic disorder and anxiety, experienced 2 safety events. The first event was an unrelated, moderate MAE of psychophysiologic insomnia assessed by the investigator to be caused by the hospitalization of the participant's girlfriend. This event occurred during the booster follow-up phase of the study (from 1 month post-booster dose through end of study). This participant's history of insomnia dated back to 2007. The participant then had an unrelated, moderate SAE of psychotic disorder with onset >3 months after booster dose and was assessed by the investigator to be due to sleep deprivation. The participant was taking trazodone for insomnia and venlafaxine for anxiety at onset of this event of psychotic disorder; these medications were discontinued during this AE and the participant was started on ziprasidone and olanzapine. This episode of psychosis resolved after 5 days. The investigator assessed that this event was unrelated to the investigational product.

Assessor's comment

Safety information for two participants who received a mixed regimen of rLP2086+MenACWY and MenABCWY has been provided by the Applicant. Both participants experienced AEs, however these were considered unrelated to the investigational products. Although this concerns a small number of participants, the information provided does not raise any safety concerns with regard to a mixed dosing schedule.

This issue is considered resolved.

4. Additional request for supplementary information

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

1. In the response to previous questions the Applicant indicates that 73 participants of Group 4 entered stage 2 of the study. Of these, 51 were enrolled in the study after the window for Visit 7. However in the CSR it is indicated that 23/73 participants in Group 4 completed Visit 7. The Applicant is asked to clarify whether this is a discrepancy.

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

MAH responses to Additional Request for supplementary information

Question 1

In the response to previous questions the Applicant indicates that 73 participants of Group 4 entered stage 2 of the study. Of these, 51 were enrolled in the study after the window for Visit 7. However, in the CSR it is indicated that 23/73 participants in Group 4 completed Visit 7. The Applicant is asked to clarify whether this is a discrepancy.

Applicant's response

This is not a discrepancy. Of the 23 participants from Group 4 that entered stage 2 who had a bleed at Visit 7, 22 were within the Visit 7 protocol window and 1 was outside the Visit 7 protocol window.

Assessor's comment
The information provided by the Applicant made clear a total of 23 participants completed Visit 7, however one was outside the protocol window. This issue is considered resolved.

5. Rapporteur's overall conclusion and recommendation

Overall, the data presented on persistence of antibodies and the anamnestic response generated by the booster vaccination 48 months after primary series are in line with the results obtained during study 1012 which are presented in the SmPC. After the booster dose, the safety profile of Trumenba was comparable to the known safety profile. No new safety signals were observed.

☒ Fulfilled:

No regulatory action required.