EMA/CHMP/374900/2024
Committee for Medicinal Products for Human Use (CHMP)

Type II variation assessment report

Procedure No. EMEA/H/C/004051/II/0053

Invented name: Trumenba

Common name: meningococcal group B vaccine (recombinant, adsorbed)

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	09 Jul 2024	09 Jul 2024
☐	CHMP Rapporteur Assessment Report	12 Aug 2024	12 Aug 2024
☐	PRAC Rapporteur Assessment Report	19 Aug 2024	19 Aug 2024
☐	PRAC members comments	23 Aug 2024	23 Aug 2024
☐	CHMP members comments	26 Aug 2024	26 Aug 2024
☐	Updated PRAC Rapporteur Assessment Report	27 Aug 2024	n/a
☐	Updated CHMP Rapporteur Assessment Report	29 Aug 2024	29 Aug 2024
☐	PRAC endorsed relevant sections of the assessment report	03 Sep 2024	03 Sep 2024
☐	Start of written procedure	03 Sep 2024	03 Sep 2024
☐	Request for Supplementary Information	05 Sep 2024	05 Sep 2024
☐	Submission of responses	18 Nov 2024	18 Nov 2024
☐	Re-start of procedure	19 Nov 2024	19 Nov 2024
☐	CHMP Rapporteur Assessment Report	16 Dec 2024	16 Dec 2024
☐	PRAC Rapporteur Assessment Report	20 Dec 2024	N/A
☐	PRAC members comments	03 Jan 2025	N/A
☐	CHMP members comments	06 Jan 2025	06 Jan 2025
☐	Updated PRAC Rapporteur Assessment Report	07 Jan 2025	N/A
☐	Updated CHMP Rapporteur Assessment Report	09 Jan 2025	N/A
☐	PRAC endorsed relevant sections of the assessment report	14 Jan 2025	N/A
☐	Start of written procedure	14 Jan 2025	14 Jan 2025
☒	Opinion	16 Jan 2024	16 Jan 2024

Table of contents

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Europe MA EEIG submitted to the European Medicines Agency on 31 May 2024 an application for a variation.

The following changes were proposed:

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

Update of sections 4.4 and 5.1 of the SmPC in order to amend an existing warning on immunocompromised individuals and to add immunogenicity data in individuals 10 years of age and above with complement deficiencies or splenic dysfunction based on final results from study B1971060 (A Phase 4, Open-Label, Single-Arm Trial to Describe the Safety, Tolerability, and Immunogenicity of Trumenba When Administered to Immunocompromised Participants ≥10 Years of Age) listed as a category 3 study in the RMP. This was an open-label, single-arm, multicenter trial in which up to 50 immunocompromised participants ≥10 years of age with asplenia (anatomic or functional) or complement deficiency have been enrolled and received bivalent rLP2086 on a 2-dose, 0- and 6-month schedule. The RMP version 8.0 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and to bring the PI in line with the latest QRD template version 10.4.

The requested variation proposed amendments to the Summary of Product Characteristics and to the Risk Management Plan (RMP).

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

Within this type II variation, the MAH intends to update information in section 4.4 to amend the existing warning for immunocompromised individuals and to add information regarding immunogenicity data in individuals ≥10 years of age with complement deficiencies or splenic dysfunction to section 5.1 of the SmPC based on the final results from study B1971060.

Study B1971060 is a phase 4, open-label, single-arm study conducted to describe the safety, and tolerability, and immunogenicity of Trumenba when administered to immunocompromised participants ≥10 years of age with asplenia (anatomic or functional) or complement deficiency. In total, 53 immunocompromised participants ≥10 years of age with asplenia (anatomic or functional) or complement deficiency were enrolled and received Trumenba on a 2-dose, 0- and 6-month schedule. The results obtained from the participants in study B1971060 were compared to a random selection of historical age and sex-matched healthy controls from study B1971057 to provide context and assist with the interpretation of the immunogenicity and safety data. Even though the historical controls were not analysed concurrently, as the serum bactericidal assay (SBA) performance and readout were similar for these 2 studies, the historical controls can be considered useful.

In total, of the 53 participants enrolled, 51 had anatomic or functional asplenia and only 2 had complement deficiency, of which only 1 participant had valid and determinate hSBA (serum bactericidal assay using human complement) titres. In these immunocompromised individuals a substantial immune response was generated, with the percentage of participants achieving hSBA titres ≥LLOQ at 1 month after Vaccination 2 ranging from 70.5% to 90.9% and the percentage of participants achieving a ≥4-fold rise in hSBA titres at 1 month after Vaccination 2 ranging from 53.5% to 76.7%. Even though the point estimates for percentage of participants achieving hSBA titres ≥LLOQ

or ≥4-fold rise at 1 month after Vaccination 2 were high in immunocompromised individuals, they trended lower compared to the healthy controls obtained from study B1971057. This is not unexpected in an immunocompromised population.

It should be noted that the level of protection afforded by achieving hSBA titres ≥LLOQ, which is a surrogate of protection in healthy individuals, might not be the same in immunocompromised individuals as Trumenba provides protection by inducing bactericidal activity via an antibody-dependent, complement-mediated pathway, and a functioning spleen is necessary for optimal phagocytosis of opsonized bacteria. However, it is likely that the immune response generated will translate into some level of protection although the effect size cannot be determined.

The limited safety database only allowed for comparison of the reactogenicity profile. The reactogenicity profile is largely comparable between immunocompromised and healthy individuals, with the majority of participants reporting local and systemic reactions. The majority of reactogenicity reactions were mild to moderate in intensity and of short duration (<3 days). Reactogenicity appeared to be slightly increased in immunocompromised individuals. This slight increase was not deemed to be clinically relevant and none of the participants discontinued due to a reactogenicity event. In addition, strong conclusions on safety profile compared to healthy individuals cannot be drawn as this entails a cross-study comparison, which is of limited value due to bias inherent in the fact that the studies are conducted in different regions, times (i.e. during the COVID pandemic or prior) and study populations.

Serious adverse events (SAEs) were reported by ~19% of participants in the immunocompromised population (n=10) after vaccination with Trumenba. None of the SAEs were considered related to Trumenba.

Overall, the submitted clinical data did not raise concerns. No new safety signals were observed.

It is agreed that the data can be added to the SmPC.

Risk Management Plan

Regarding the missing information "Use in immunocompromised individuals (e.g., individuals with terminal complement deficiency or asplenia)": overall the submitted data did not raise concerns. The PRAC agreed to remove it from the RMP. The PRAC also agreed with the removal of "Vaccine effectiveness" as missing information following procedure No. EMEA/H/C/006165/0000.

The benefit-risk balance of Trumenba, remains positive.

3. Recommendations

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

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

Update of sections 4.4 and 5.1 of the SmPC in order to amend an existing warning on immunocompromised individuals and to add immunogenicity data in individuals 10 years of age and above with complement deficiencies or splenic dysfunction based on final results from study B1971060; listed as a category 3 study in the RMP. This was an open-label, single-arm, multicentre trial in which up to 50 immunocompromised participants ≥10 years of age with asplenia (anatomic or

functional) or complement deficiency have been enrolled and received Trumenba on a 2-dose, 0- and 6-month schedule. The RMP version 8.0 has been approved. In addition, the MAH took the opportunity to introduce minor editorial changes to the SmPC.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex I and to the Risk Management Plan are recommended.

4. EPAR changes

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

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Trumenba-H-C-4051-II-0053'

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

5. Introduction

Trumenba is a bivalent recombinant lipoprotein 2086 vaccine (bivalent rLP2086) that consists of 2 purified recombinant lipoprotein 2086 (rLP2086) antigens, i.e. 1 protein antigen from each of the factor H binding protein (fHBP) subfamilies (A and B), of *N. meningitidis* serogroup B. The fHBP protein is found on the surface of meningococcal bacteria and is essential for bacteria to avoid host immune defences and >95% of serogroup B strains express fHBPs from either subfamily.

Trumenba was approved in the European Union (EU) on 24 May 2017 and is indicated for active immunisation to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B in individuals 10 years and older. The posology of the primary series consists of 2 doses administered at a 6-month interval or 3 doses, with the first 2 doses administered at least 1 month apart followed by a third dose at least 4 months after the second dose.

With the present submission the MAH intends update sections 4.4 and 5.1 of the SmPC in order to amend an existing warning on immunocompromised individuals and to add immunogenicity data in individuals 10 years of age and above with complement deficiencies or splenic dysfunction based on final results from study B1971060. This study was listed as a category 3 study in the RMP.

Study B1971060 is a phase 4, open-label, single-arm study conducted to describe the safety, and tolerability, and immunogenicity of Trumenba when administered to immunocompromised participants ≥10 years of age with asplenia (anatomic or functional) or complement deficiency.

Individuals with anatomic asplenia or functional asplenia (e.g., sickle cell anaemia) or complement deficiencies (including but not limited to deficiencies in C5-C9, properdin, factor D, or factor H) are known to be at increased risk of severe infections caused by encapsulated bacteria, including *S pneumoniae*, *Neisseria meningitidis*, and H influenza type B.

S pneumoniae, N meningitidis, and H influenza type B (Hib) account for more than half of the severe bacterial infections in asplenic individuals, and the lifetime risk of infection is higher in children than in adults. It is therefore important to protect immunocompromised individuals, particularly those with asplenia or complement deficiencies, against encapsulated bacterial pathogens, such as N meningitidis, because of the increased risk of morbidity and mortality.

6. Clinical Efficacy aspects

The application is based on the final study report of study B1971060. This was a Phase 4, open-label, single-arm, multicentre trial in which 53 immunocompromised participants ≥10 years of age (no upper age limit proposed) with asplenia (anatomic or functional) or complement deficiency were enrolled and received Trumenba on a 2-dose, 0- and 6-month schedule. All participants were to be naive to any meningococcal serogroup B vaccine prior to enrolment.

Historical data from age- and sex-matched healthy participants from the previously completed pivotal Phase 3 MenB study (B1971057) were used as a reference for the safety and immunogenicity of Trumenba in the general population. Study B1971057 followed the same 0- and 6-month dosing schedule and used the same methodology for assessment of immunogenicity and safety as those for Study B1971060. Healthy adolescents and young adults (10 to <26 years of age) from Study B1971057 were randomly selected to serve as controls.

A study schedule is presented below.

	Vaccination 1	Safety Follow-up Visit	Vaccination 2	Post–Vaccination 2 Blood Draw	Telephone Contact
Visit ID	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Approximate month	0	1	6	7	12
Vaccination	Trumenba		Trumenba		
Blood draw	20 mL			20 mL	

Rapporteur's Assessment

Individuals with anatomic or functional asplenia or complement deficiency are known to be at increased risk of severe infections caused by encapsulated bacteria, including *N. meningitidis*. The currently submitted study was used to evaluate the immunogenicity and safety/tolerability of a 2-dose schedule of Trumenba in individuals with impaired splenic activity or complement deficiency. Usually, the immune response in immunocompromised subjects is lower than in heathy subjects.

Study B1971057 demonstrated that 2 doses of Trumenba administered on a 0- and 6-month schedule to healthy adolescents and adults ≥10 to <26 years of age are safe and well tolerated and elicit a robust functional immune response. As study B1971060 will also use this dosing regimen, the use of historical age and sex-matched healthy controls from study B1971057 to provide context and assist with the interpretation of the immunogenicity and safety data is appreciated. However, the samples from the historical control were not measured again concurrently with the samples of the current study. The MAH was requested to clarify that there were no relevant differences in the assay conduction. The MAH confirmed that the assays were performed in the same laboratories for both study B1971060 and B1971057. Although all reagents were replaced, which is to be expected as there is a 4-year gap between studies, reagents were qualified and bridged to prior qualified lots. The most reassuring information is that long-term SBA performance is monitored using one panel of sera per test strain with titres across the validated assay range. The titres of the panel acquired during performance of the 2 studies were comparable for all 4 primary MenB test strains. This indicates that SBA performance and readout were comparable for these 2 studies. Therefore, the controls are regarded as useful.

6.1. Methods – analysis of data submitted

Study population

The study population consists of male or female immunocompromised subjects ≥ 10 years of age. Immunocompromised participants are defined as individuals at increased risk for meningococcal disease due to anatomic asplenia or functional asplenia (e.g., sickle cell anaemia) or complement deficiencies (including but not limited to deficiencies in C5-C9, properdin, factor H or factor D).

In addition to standard exclusion criteria, subjects presenting with any of the following were ineligible to be included in the study:

1. History of microbiologically proven disease caused by *N. meningitidis* or *N. gonorrhoeae*.
2. Any confirmed or suspected human immunodeficiency virus infection, based on medical history and physical examination (no laboratory testing required).
3. Previous vaccination with any meningococcal serogroup B vaccine.

4. Participants who are receiving any allergen immunotherapy with a non-licensed product or receiving allergen immunotherapy with a licensed product and are not on stable maintenance doses.
5. Receipt of immunoglobulin infusion or injection during the 42 days preceding enrolment.
6. Current chronic use of systemic antibiotics.
7. Previous receipt or current use of complement inhibitors (e.g., eculizumab, ravulizumab).
8. Participation in other studies involving investigational drug(s) within 28 days prior to study entry and/or during study participation.

Moreover, criteria for temporarily delaying vaccine administration were also defined. These conditions are temporary or self-limiting and a subject may be vaccinated once the conditions have resolved.

Rapporteur's Assessment

The study population seems adequately described. Participants should have anatomic asplenia, functional asplenia (e.g., sickle cell anaemia) or complement deficiencies. Only participants with absolute functional asplenia were allowed to be enrolled, as liver-spleen scan with no splenic uptake was required for potential subjects with conditions other than sickle cell disease that can be associated with different degrees of functional hyposplenia. As worst-case scenario, absolute asplenia, was investigated, extrapolation to other splenic dysfunctions can be acceptable.

Extrapolation of data from this population to other immunocompromised populations (e.g. participants treated with high doses of corticosteroids) is limited. The fact that only participants with complement deficiencies and splenic dysfunctions were included in the study is covered in the SmPC.

All individuals meeting the underlying condition criteria for inclusion might benefit from the vaccination, therefore, ethically, should be allowed to enrol. For immunocompromised participants older than 25 years of age in this study, the controls will be randomly selected from the group of participants 25 years of age from Study B1971057. The control group may therefore be a bit younger than the immunocompromised group, which could be acceptable as this would represent a worst-case scenario.

Treatments

The study intervention was Trumenba (the term bivalent rLP2086 and meningococcal serogroup B vaccine [Trumenba] may be used interchangeably). Trumenba is a 0.5 mL dose supplied as a PFS and formulated to contain 60 µg each of a purified subfamily A and a purified subfamily B rLP2086 protein. Other components include sodium chloride, polysorbate 80, and Al3+ as AlPO4 in histidine-buffered saline at pH 6.0.

Participants will be administered Trumenba by intramuscular injection into the upper deltoid muscle of the left arm at Months 0 and 6 (Visit 1 and 3).

Rapporteur's Assessment

Commercial Trumenba was administered 6 months apart as recommended in the SmPC for the 2-dose schedule.

Objectives and Endpoints

The estimands corresponding to each primary and exploratory immunogenicity objective are described in Table 1. The estimands to evaluate the immunogenicity objectives are based on evaluable populations. These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Additional analyses are specified as well, including participants regardless of whether or not the participants followed the study schedules.

Table 1 List of Primary and Exploratory Immunogenicity Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary Immunogenicity:	**Primary Immunogenicity:**	**Primary Immunogenicity:**
• To describe the immune response induced by 2 doses of Trumenba in immunocompromised participants and historical age- and sex-matched healthy participants as measured by hSBA performed with 4 primary MnB test strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein.	In immunocompromised participants or historical age- and sex-matched healthy participants who are separately receiving 2 doses of study intervention and are in compliance with key protocol criteria (evaluable participants): • The proportion of participants with hSBA titer ≥ LLOQ (1:16 for A22 and 1:8 for A56, B24, and B44) for each of the 4 primary MnB test strains 1 month after Vaccination 2.	• hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44).
Exploratory Immunogenicity:	**Exploratory Immunogenicity:**[a]	**Exploratory Immunogenicity:**
• To further describe the immune response induced by 2 doses of Trumenba in immunocompromised participants and historical age- and sex-matched healthy participants.	In immunocompromised participants or historical age- and sex-matched healthy participants separately who are receiving 2 doses of study intervention and are in compliance with key protocol criteria (evaluable participants): • The proportion of participants achieving a 4-fold rise in hSBA titer from baseline for each of the 4 primary MenB test strains 1 month after Vaccination 2.	• hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44).

[a] The exploratory objective to further describe the immune response induced by 2 doses of Trumenba related to 4-fold rises from baseline was not included in the protocol but described in the SAP. Additionally, after completion of the planned analyses for the CSR, the following additional analyses not in the SAP were conducted for each of the test strains: (1) GMTs and (2) the proportion of participant achieving hSBA titres of ≥1:4, ≥ 1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:28, as requested in the EMA Assessment Reports concerning the B1971060 protocol and SAP which stated that analyses of these additional endpoints would be expected to be presented in the final CSR.

Rapporteur's Assessment

The immunogenicity objectives and additional analyses are considered adequate to describe the immune response generated by 2-dose (0- and 6-month) regimen of Trumenba in immunocompromised participants.

The estimand is not described according to ICH E9 (R1) guideline (Addendum on estimands and sensitivity analysis in clinical trials). Especially the strategy regarding missing information due to intercurrent events is lacking. It is expected that the MAH will describe and predefine estimands more thoroughly in future submissions.

Sample size

This was a descriptive study. The study sample size is not based on any hypothesis-testing criteria. The study aimed to enrol up to 50 participants to allow for sufficient numbers when describing findings

with regard to this particular population. Immunogenicity and safety are reported descriptively for the immunocompromised participants and historical age- and sex-matched healthy control participants.

Rapporteur's Assessment

This is a descriptive study and sample size was not based on hypothesis testing. The study will enrol 50 immunocompromised patients and 50 historical matched controls, which could be sufficient to allow for a relevant comparison of the immunogenicity profile in immunocompromised patients and healthy participants. The sample size is too small to detect rare adverse events. However, it will be sufficient to allow for a comparison of the reactogenicity profile of Trumenba in immunocompromised patients and healthy controls.

Randomisation and Blinding (masking)

This will be an open-label, single-arm study – participants will not be randomised to vaccine assignment.

Rapporteur's Assessment

The study is designed as a single-arm open-label study. This can be accepted as the primary endpoint is an objective measurement (measurement of antibodies), therefore it is not expected that this endpoint will be influenced by the open-label design. The results of the subjective safety parameters should be interpreted with care.

Statistical methods

Descriptive summary statistics will be provided for all endpoints. Unless otherwise explicitly stated, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum. Descriptive statistics for categorical variables are the proportion (%) and the n (the numerator) and N (the denominator) used in the calculation of the proportion. The analyses for binary endpoints will summarize the number and percentage of participants in each category. The exact 2-sided 95% CIs for percentages, and for difference in percentages, will also be presented, where appropriate. The exact 2-sided 95% CIs for the proportion will be constructed by the Clopper-Pearson method described by Agresti. The exact 2-sided 95% CIs will be presented in terms of percentages.

Methods to Manage Missing Data

Safety Data

Standard algorithms for handling missing AE start dates will be applied according to Pfizer safety rules. No other missing information will be imputed in the safety analysis. If the withdrawal rate of Study B1971060 exceeds 15%, then an additional sensitivity analysis will be planned to study the percentage of participants who either withdraw from the study or have an AE. This is to be done descriptively to show the results separately for immunocompromised participants and age- and sex-matched healthy controls.

For derived variables based on reactogenicity data, if any day of the 7-day e-diary data are available, the "any day (Days 1-7)" data will be considered non-missing. Participants are excluded from the analysis if they do not receive the particular dose or the safety data are missing on all days within the interval.

The reactogenicity data are collected through the e-diary, which does not allow participants to skip the question. Therefore, for a specific day, as long as the e-diary data are transferred for that day, all of the reactogenicity data for the participant on that day are non-missing. The e-diary transmission and completion status will be summarized per Section 6.5.4. The e-diary completion summary will provide the missing data information on the reactogenicity data.

Based on the available study data from the bivalent rLP2086 development program, missing reactogenicity data are negligible, which is consistent with Li et al (2011).2 No sensitivity analysis is planned for reactogenicity data.

Immunogenicity Data

As assay data are expected to be missing completely at random, the primary analysis for the primary objectives will be based upon the observed, determinate observations. No imputation will be performed. The proportion of participants with missing immunogenicity data may be summarized at each blood sampling visit for the hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44). The denominator will be the number of participants randomized. The category of missing reasons (QNS, indeterminate, not done, dropout) may also be summarized.

Both the evaluable population and the mITT population will be used for the analysis of immunogenicity results. Missing serology results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis. For the hSBA results, the following values will be set to missing: QNS (insufficient sera), indeterminate results, and not done. Participants without blood draw (i.e., dropout) will also be considered to have missing data for immunogenicity.

Analysis sets

The analysis populations were defined as shown in Table 2

Table 2 Description of analysis sets

Population	Description
mITT	All participants who have at least 1 valid and determinate MnB assay result available at any time point from Day 1 through 1 month after the second vaccination (Visit 4 for this study).
Evaluable immunogenicity	All participants who • Were eligible through 1 month after Vaccination 2. • Received the study intervention at Visit 1 and Visit 3 as randomised. • Had blood drawn for assay testing within the required time frames at Visit 1 (before Vaccination 1) and 1 month after Vaccination 2 (28-42 days after Visit 3). • Had at least 1 valid and determinate assay result 1 month after Vaccination 2. • Received no prohibited vaccines or medications through Visit 4. • Had no major protocol deviations through Visit 4.
Safety	All enrolled participants who received at least 1 dose of the study intervention and have safety data reported after vaccination.
Vaccination 1 safety	All participants who received the first dose of study intervention at Visit 1 and for whom safety information is available from Visit 1 to prior to Visit 3.
Vaccination 2 safety	All participants who received the second dose of study intervention at Visit 3 and for whom safety information is available from Visit 3 up to and including Visit 4.
Follow-up safety	All participants who received at least 1 dose of study intervention and for whom safety information is available from after Visit 4 up to and including Visit 5.

Rapporteur's Assessment

This is a descriptive study. No hypothesis testing will be performed. This is considered appropriate for the aim of this study: describing the immune response in participants with anatomic asplenia or functional asplenia (e.g., sickle cell anaemia) or complement deficiencies.

6.2. Results

Participant flow

All 53 (100.0%) immunocompromised participants enrolled in Study B1971060 received Vaccination 1 compared with 51 (96.2%) healthy controls in Study B1971057 (Figure 1). Among enrolled participants in each study, 47 (88.7%) received Vaccination 2 and completed the vaccination phase.

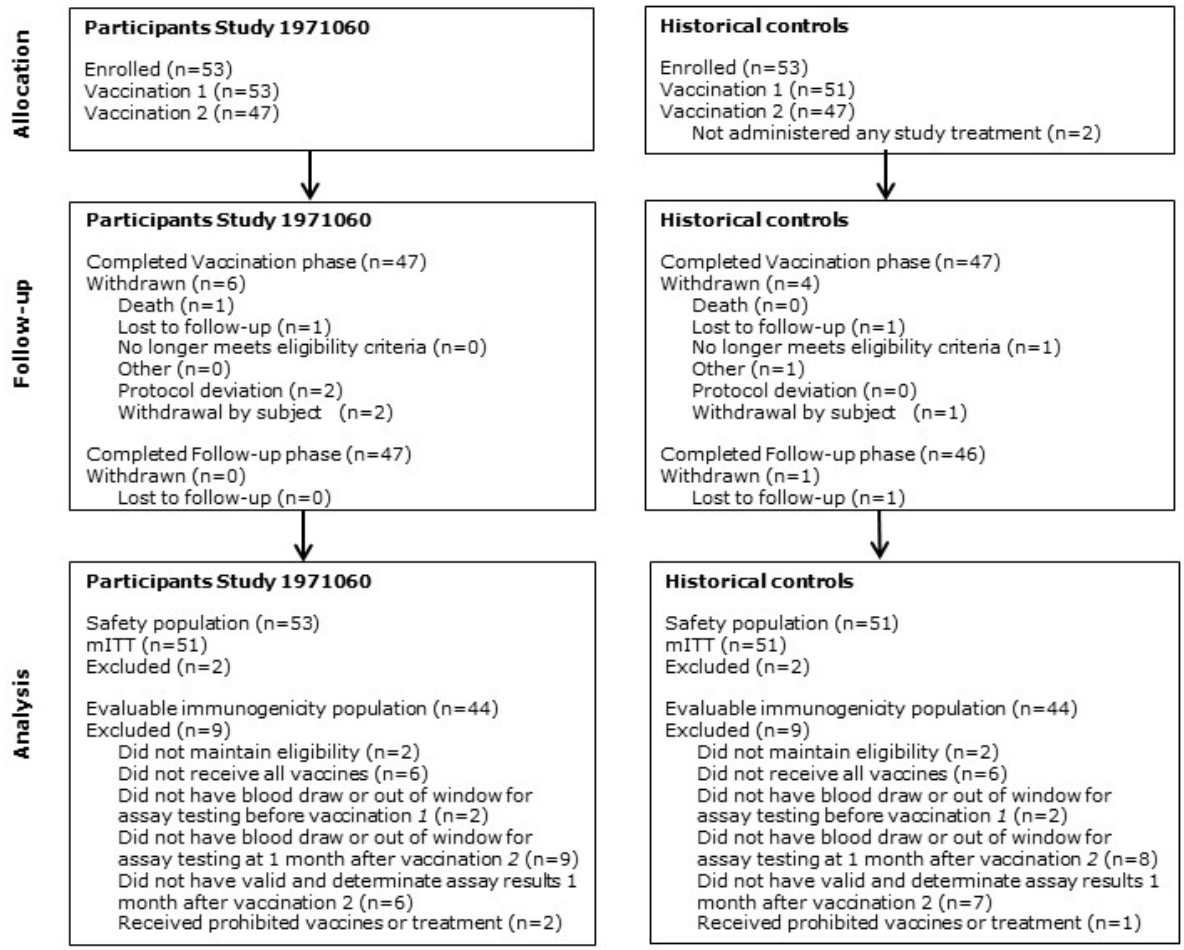


Figure 1 Participant flow of study B1971060 and the historical controls

Rapporteur's Assessment

The majority of the participants in study B1971060 were vaccinated, with 53 (100%) receiving vaccination 1 and 47 (88.7%) receiving vaccination 2. In total 88.7% completed the study.

The disposition of participants and evaluable populations are comparable between the current study and the historical controls.

No concerns arise.

Recruitment

The first participant first visit occurred on 18 August 2021 and the last subject last visit was on 06 September 2023.

The study was conducted at 10 sites in the Czech Republic, Poland, and Turkey. The 2 sites planned in the US did not enrol any immunocompromised participants.

Rapporteur's Assessment

Study B1971057 was conducted in sites in Czech Republic, Finland, Poland and the United States.

No concerns arise.

Conduct of the study

Protocol amendments

Study B1971060 started enrolment under the final version of the protocol dated 22 January 2021, this protocol version was assessed in procedure EMEA/H/C/004051/MEA/003.5. No amendments were implemented after enrolment started.

Protocol deviations

Important protocol deviations (PDs), defined as PDs that may significantly impact the completeness, accuracy, and/or reliability of the trial data or that may significantly affect a participant's rights, safety, or well-being are summarized below.

Among immunocompromised participants:

- Two participants met exclusion criterion #8, i.e., was previously vaccinated with any meningococcal serogroup B vaccine (the investigator became aware only after enrolment).
- Three participants completed their Visit 4 (post-Vaccination 2 blood draw) outside of the visit window.
- One participant received prohibited systemic (oral, intravenous, or intramuscular) corticosteroid therapy within 28 days before through 28 days after any study vaccination.

Among healthy controls:

- One participant completed a visit 2 days outside of the visit window for Visit 4 (post- Vaccination 2 blood draw).
- One participant, on 2 occasions, received systemic antibiotic therapy within 5 days prior to having blood drawn for immunogenicity testing, thus meeting criteria for temporary delay of the immunogenicity blood draw; however, the blood draw was not temporarily delayed.

Rapporteur's Assessment

There were no protocol adjustments from time of first participant first visit to last subject visit.

The participants with important protocol deviations should not be included in the evaluable immunogenicity population, however, they should be included in the mITT.

Baseline data

The baseline demographic data is shown in Table 3. The mean age at vaccination was 32.5 years for immunocompromised participants and 22.2 years in healthy controls. The difference in mean ages between immunocompromised participants arise from the different age eligibility for each study (≥10 years for Study B1971060 and 10 to <26 years of age for Study B1971057), with 19% of immune-compromised participants older than 50 years of age. For immunocompromised participants older than 25 years of age in this study, the age- and sex-matched heathy controls were randomly selected from participants of the same sex at 25 years of age from Study B1971057.

Table 3 Demographic Characteristics – Safety Population

	Trumenba (B1971060) (N[a]=53) n[b] (%)	**Vaccine Group (as Administered) Historical Age- and Sex-Matched Controls (Trumenba + Menveo) (B1971057) (N[a]=51) n[b] (%)**
Sex		
Male	30 (56.6)	30 (58.8)
Female	23 (43.4)	21 (41.2)
Race		
White	53 (100.0)	46 (90.2)
Black or African American	0	3 (5.9)
Asian	0	2 (3.9)
Ethnicity		
Hispanic or Latino	0	7 (13.7)
Not Hispanic or Latino	53 (100.0)	44 (86.3)
Geographic location		
US	0	42 (82.4)
Ex-US	53 (100.0)	9 (17.6)
Age at Vaccination 1 (years)		
Mean (SD)	32.5 (16.55)	22.2 (4.26)
Median	25.0	25.0
Min, max	(10.0, 69.0)	(10.0, 25.0)

Abbreviation: Ex-US = global, not including the United States.

Note: The 2 participants in the B1971057 control group were randomized but withdrew before any vaccination.

a. N = number of participants in the specified group, or the total sample. This value is used as the denominator for the
percentage calculations.

b. n = Number of participants with the specified characteristic.

Rapporteur's Assessment

The fact that 19% of participants was >50 years of age in the immunocompromised population could potentially impact the results of this group. It is known that with increasing age, from approximately 50 years of age onwards, the immune response decreases.

It should be noted that all participants in the immunocompromised population were derived from Ex-US, while the vast majority of the historical controls were enrolled in the US. This could influence baseline seropositivity. In addition, differing epidemiology could affect the responses seen.

Numbers analysed

Table 4 provides a summary of the number of randomized participants that were included in- and excluded from the immunogenicity populations.

Table 4 Immunogenicity Populations

	Trumenba (B1971060) n[a] (%)	Historical age-and sex-matched controls (Trumenba +Menveo) (B1971057) n[a] (%)
Randomised[b]	53	53
mITT population	51 (96.2)	51 (96.2)
Excluded from mITT population	2 (3.8)	2 (3.8)
Evaluable immunogenicity population	44 (83.0)	44 (83.0)
Excluded from evaluable immunogenicity population	9 (17.0)	9 (17.0)
Reason for exclusion[c]		
Did not maintain eligibility, based on criteria up until and including Visit 4	2 (3.8)	2 (3.8)
Did not receive all investigational products as randomized	6 (11.3)	6 (11.3)
Did not have blood draw or was out of window for assay testing before Vaccination 1	2 (3.8)	2 (3.8)
Did not have blood draw or was out of window for assay testing at 1month after Vaccination 2	9 (17.0)	8 (15.1)
Did not have valid and determinate assay results at 1 month after Vaccination 2	6 (11.3)	7 (13.2)
Received prohibited vaccines or treatment through Visit 4	2 (3.8)	1 (1.9)

Rapporteur's Assessment

The percentage of participants excluded from the evaluable population was comparable between study B1971060 and the historical controls.

Outcomes and estimation

Primary immunogenicity endpoint: Participants Achieving hSBA Titer ≥ LLOQ

The results for the evaluable immunogenicity population are presented in Table 5. Responses for the mITT population were similar to those observed for the evaluable population. It should be noted that the evaluable immunogenicity population comprised asplenic participants and only 1 complement-deficient participant.

Table 5 Number (%) of Participants with hSBA Titer ⩾ LLOQ for Each of the 4 Primary MenB Strains – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)							
	Trumenba (B1971060)				Historical Age- and Sex-Matched Controls (Trumenba + Menveo) (B1971057)			
MenB Strain (Variant) Time Point	N[a]	n[b]	(%)	(95% CI)[c]	N[a]	n[b]	(%)	(95% CI)[c]
PMB80 (A22)								
Before Vaccination 1	43	14	(32.6)	(19.1, 48.5)	42	13	(31.0)	(17.6, 47.1)
1 Month after Vaccination 2	44	33	(75.0)	(59.7, 86.8)	43	41	(95.3)	(84.2, 99.4)
PMB2001 (A56)								

MenB Strain (Variant) Time Point	Vaccine Group (as Randomized) Trumenba (B1971060) Na	nb	(%)	(95% CI)c	Historical Age- and Sex-Matched Controls (Trumenba + Menveo) (B1971057) Na	nb	(%)	(95% CI)c
Before Vaccination 1	43	11	(25.6)	(13.5, 41.2)	43	10	(23.3)	(11.8, 38.6)
1 Month after Vaccination 2	44	40	(90.9)	(78.3, 97.5)	44	44	(100.0)	(92.0, 100.0)
PMB2948 (B24)								
Before Vaccination 1	42	1	(2.4)	(0.1, 12.6)	43	10	(23.3)	(11.8, 38.6)
1 Month after Vaccination 2	44	31	(70.5)	(54.8, 83.2)	44	36	(81.8)	(67.3, 91.8)
PMB2707 (B44)								
Before Vaccination 1	43	4	(9.3)	(2.6, 22.1)	44	5	(11.4)	(3.8, 24.6)
1 Month after Vaccination 2	43	34	(79.1)	(64.0, 90.0)	42	39	(92.9)	(80.5, 98.5)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation. MenB = *Neisseria meningitidis* group B.
Note: LLOQ = 1:16 for A22; 1:8 for A56, B24, and B44.
a. N = number of participants with valid and determinate hSBA titres 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.

Rapporteur's Assessment

The percentage of participants achieving a hSBA Titer ≥ LLOQ was substantial for all 4 primary MenB strains in the immunocompromised population, ranging from 70.5% to 90.9%. The point estimates for the percentage of participants achieving a hSBA Titer ≥ LLOQ trended lower in the immunocompromised population versus the historical controls. This is not unexpected for an immunocompromised population. However, it might also have been impacted by age. The age in the immunocompromised population was higher compared to the historical controls. In total, 19% of participants was >50 years of age in the immunocompromised population. The MAH presented the immunogenicity results (including the exploratory analyses) for immunocompromised participants <50 and ≥50 years of age separately. No clear impact of age was observed, indicating that the lower immune-response was mainly driven by the underlying immunocompromising disease.

It is reassuring that the results in the mITT population were comparable to the results in the evaluable population, with percentage of participants achieving a hSBA Titer ≥ LLOQ for PMB80 being 76.6% (95%CI: 62.0, 87.7), PMB2001 being 89.4% (95%CI: 76.9, 96.5), PMB2948 being 68.1% (95%CI: 52.9, 80.9) and PMB2707 being 78.3% (95%CI: 63.6, 89.1).

It should be noted that 1 out of 42 participants (2.4%) already had a hSBA Titer ≥ LLOQ for PMB2948 (B24), while this was the case for 10 out of 43 (23.3%) in the historical control group. This could be due to differing epidemiology based on geographical location and time at which study was performed.

Only 1 complement-deficient participant attributed to the results.

Exploratory results

The proportions of immunocompromised participants achieving ≥4-fold rise in hSBA titres at 1 month after Vaccination 2 are presented in Table 6. Responses for the mITT population were similar to those observed for the evaluable population.

Table 6 Number (%) of Participants Achieving ≥ 4-Fold Rise in hSBA Titer for Each of the 4 Primary MenB Strains – Evaluable Immunogenicity Population

Endpoint MenB Strain (Variant) Time Point	Vaccine Group (as Randomized) Trumenba (B1971060) Na	nb	(%)	(95% CI)c	Historical Age- and Sex-Matched Controls (Trumenba + Menveo) (B1971057) Na	nb	(%)	(95% CI)c
PMB80 (A22)								
1 Month after Vaccination 2	43	23	(53.5)	(37.7, 68.8)	41	31	(75.6)	(59.7, 87.6)
PMB2001 (A56)								
1 Month after Vaccination 2	43	33	(76.7)	(61.4, 88.2)	43	39	(90.7)	(77.9, 97.4)
PMB2948 (B24)								
1 Month after Vaccination 2	42	28	(66.7)	(50.5, 80.4)	43	28	(65.1)	(49.1, 79.0)
PMB2707 (B44)								
1 Month after Vaccination 2	42	29	(69.0)	(52.9, 82.4)	42	33	(78.6)	(63.2, 89.7)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; LOD = limit of detection; MenB = *Neisseria meningitidis* group B.
Note: LLOQ = 1:16 for A22; 1:8 for A56, B24, and B44.
Note: The 4-fold increase is defined as follows: (1) For participants with a baseline hSBA titer below the LOD (hSBA titer 1:4), a response is defined as an hSBA titer ≥ 1:16 or the LLOQ (whichever titer is higher). (2) For participants with a baseline hSBA titer ≥ LOD and < LLOQ, a response is defined as an hSBA titer ≥ 4 times the LLOQ. (3) For participants with a baseline hSBA titer ≥ LLOQ, a response is defined as an hSBA titer ≥ 4 times the baseline titer.
a. For hSBA titer fold rise, N = number of participants with valid and determinate hSBA titres for the given strain at both the specified time point and baseline.
b. For hSBA titer fold rise, n = number of participants who achieved hSBA titer fold rise ≥4 from baseline for the given strain.
c. Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.

Rapporteur's Assessment

The percentage of participants achieving a 4-fold rise in hSBA titres was substantial for all 4 primary MenB strains in the immunocompromised population, ranging from 53.5% to 76.7%. Again, the point estimates for the percentage of participants achieving a 4-fold rise in hSBA titres trended lower in the immunocompromised population versus the historical controls (ranging from 65.1% to 90.7%).

The results in the mITT population were comparable to the results in the evaluable population for fold-rise in hSBA titres, indicating that the results of the study are robust.

In the evaluable immunogenicity population, hSBA GMTs increased substantially from baseline to 1 month after Vaccination 2 for the 4 primary MenB test strains in both immunocompromised (range: 4.1 to 14.3 at baseline; 17.9 to 97.9 after Vaccination 2) and healthy controls (range: 5.4 to 12.5 at baseline; 24.9 to 142.9 after Vaccination 2) (Table 7). Responses for the mITT population were similar to those observed for the evaluable population.

Table 7 hSBA GMTs at Baseline and 1 Month After Vaccination 2 for Each of the 4 Primary MenB Strains – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)					
	Trumenba (B1971060)			Historical Age- and Sex-Matched Controls (Trumenba + Menveo) (B1971057)		
MenB Strain (Variant) Time Point	**N[a]**	**GMT[b]**	**(95% CI[c])**	**N[a]**	**GMT[b]**	**(95% CI[c])**
PMB80 (A22)						
Before Vaccination 1	43	14.3	(10.9, 18.8)	42	12.5	(9.9, 15.8)
1 Month after Vaccination 2	44	41.2	(28.9, 58.6)	43	54.5	(39.5, 75.2)
PMB2001 (A56)						
Before Vaccination 1	43	8.1	(5.2, 12.7)	43	6.9	(4.8, 10.0)
1 Month after Vaccination 2	44	97.9	(60.6, 158.1)	44	142.9	(101.4, 201.4)
PMB2948 (B24)						
Before Vaccination 1	42	4.1	(3.9, 4.2)	43	6.3	(4.7, 8.4)
1 Month after Vaccination 2	44	17.9	(12.4, 25.7)	44	24.9	(16.9, 36.7)
PMB2707 (B44)						
Before Vaccination 1	43	4.6	(3.9, 5.3)	44	5.4	(4.1, 7.1)
1 Month after Vaccination 2	43	30.5	(19.5, 47.7)	42	39.7	(26.9, 58.5)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; MenB = *Neisseria meningitidis* group B.
Note: LLOQ = 1:16 for A22; 1:8 for A56, B24, and B44. Results below the LLOQ were set to 0.5 × LLOQ for analysis.
a. N = number of participants with valid and determinate hSBA titres for the given strain.
b. GMTs were calculated using all participants with valid and determinate hSBA titres at the given time point.
c. CIs are obtained by exponentiating the limits of Cis for the mean logarithm of the hSBA titres (based on the Student t distribution).

Rapporteur's Assessment

The hSBA titres increased substantially after vaccination for all 4 primary MenB strains in the immunocompromised population. Even though the point estimates for the hSBA titres trended lower in the immunocompromised population versus the historical controls, there still was substantial overlap.

The results in the mITT population were comparable to the results in the evaluable population for GMTs, indicating that the results of the study are robust.

The RCDCs for the evaluable immunogenicity population (Figure 2) show that high proportions of immunocompromised participants and healthy controls achieved ≥ LLOQ for each MenB primary test strain at 1 month after Vaccination 2.

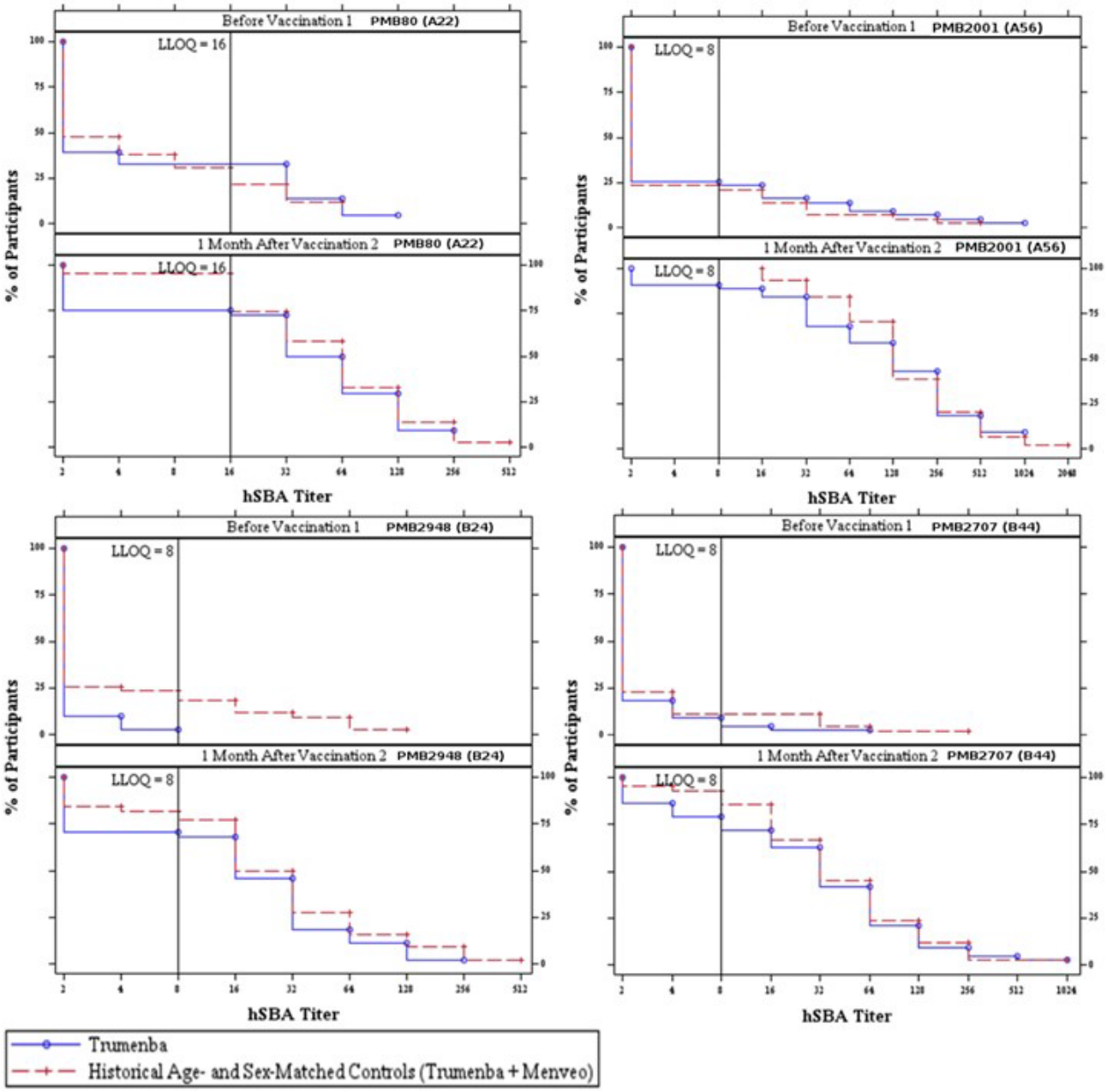


Figure 2 Reverse-Cumulative Distribution Curves –Trumenba and Age and Sex-Matched Controls (Trumenba + Menveo) – Evaluable Immunogenicity Population

Rapporteur's Assessment

The RCDCs reflect that the hSBA titres substantially increase after vaccination in both the immunocompromised population and historical controls. The response is largely comparable in the immunocompromised population to the historical controls.

6.3. Discussion

The purpose of this submission is to update information in section 4.4 to amend the existing warning for immunocompromised individuals and to add information regarding immunogenicity data in individuals ≥10 years of age with complement deficiencies or splenic dysfunction to section 5.1 of the

SmPC based on the final results from study B1971060.

Design and conduct of clinical studies

Study B1971060 is a phase 4, open-label, single-arm study conducted to describe the safety, and tolerability, and immunogenicity of Trumenba when administered to immunocompromised participants ≥10 years of age with asplenia (anatomic or functional) or complement deficiency. In total, 53 immunocompromised participants ≥10 years of age with absolute asplenia (anatomic or functional) or complement deficiency were enrolled and received Trumenba on a 2-dose, 0- and 6-month schedule. The results obtained from the participants in study B1971060 were compared to a random selection of historical age and sex-matched healthy controls from study B1971057 to provide context and assist with the interpretation of the immunogenicity and safety data. However, the samples from the historical control were not measured again concurrently with the samples of the current study. The MAH was requested to clarify that there were no relevant differences in the assay conduction. The MAH confirmed that the assays were performed in the same laboratories for both study B1971060 and B1971057. In addition, long-term SBA performance is monitored using one panel of sera per test strain with titres across the validated assay range. The titres of the panel acquired during performance of the 2 studies were comparable for all 4 primary MenB test strains, indicating that SBA performance and readout were comparable for these 2 studies. Therefore the controls are regarded as useful.

In general terms, the study design is appropriate, as the immunogenicity endpoints are objective measures not influenced by the open-label nature of the study. Caution should be used when interpreting the safety data. The immunogenicity objectives and additional analyses are considered adequate to describe the immune response generated by 2-dose (0- and 6-month) regimen of Trumenba in immunocompromised participants. The sample size, 50 participants, is sufficient to allow for a relevant comparison of the immunogenicity profile in immunocompromised patients and healthy participants. For immunocompromised participants older than 25 years of age in this study, the controls will be randomly selected from the group of participants 25 years of age from Study B1971057, which is appropriate as this would represent a worst-case scenario. Only participants with absolute functional asplenia were allowed to be enrolled, which would allow extrapolation to other splenic dysfunctions.

Extrapolation of data from this population to other immunocompromised populations (e.g. participants treated with high doses of corticosteroids) is limited. The fact that only participants with complement deficiencies and splenic dysfunctions were included in the study is covered in the SmPC.

Efficacy data and additional analyses

In total, of the 53 participants enrolled, 51 had anatomic or functional asplenia and only 2 had complement deficiency, of which only 1 participant had valid and determinate hSBA titres. In this immunocompromised population a substantial immune response was generated, with the percentage of participants achieving hSBA titres ⩾LLOQ at 1 month after Vaccination 2 ranging from 70.5% to 90.9% and the percentage of participants achieving a ⩾4-fold rise in hSBA titres at 1 month after Vaccination 2 ranging from 53.5% to 76.7%. Even though the point estimates for percentage of participants achieving hSBA titres ⩾LLOQ or ⩾4-fold rise at 1 month after Vaccination 2 were high in immunocompromised individuals, they trended lower compared to the healthy controls obtained from study B1971057. This is not unexpected in an immunocompromised population. It might also be influenced by the fact that 19% of participants in study B1971060 were ⩾50 years of age. It is known that with increasing age, from approximately 50 years of age, the immune response decreases. The MAH presented the immunogenicity results (including the exploratory analyses) for

immunocompromised participants <50 and ≥50 years of age separately. No clear impact of age was observed, indicating that the lower immune response was mainly driven by the underlying immunocompromising disease.

The results of the hSBA GMTs are in line with the proportion of participants achieving hSBA titres ≥LLOQ and were visualised in reverse cumulative distribution curves. The results in the mITT population were comparable to the results in the evaluable population for fold-rise in hSBA titres, indicating that the results of the study are robust.

It should be noted that the level of protection afforded by achieving hSBA titres ≥LLOQ, which is a surrogate of protection in healthy individuals, might not be the same in immunocompromised individuals as Trumenba provides protection by inducing bactericidal activity via an antibody-dependent, complement-mediated pathway, and a functioning spleen is necessary for optimal phagocytosis of opsonized bacteria.

Overall, a substantial immune response was observed in immunocompromised population following a 2-dose regimen of Trumenba that was slightly reduced compared to historical controls. It can be assumed that this immune response will likely translate into some level of protection. However, it is not possible to determine the exact effect size and clinical level of protection.

7. Clinical Safety aspects

The safety profile of Trumenba has been established in children aged 10 years and older, adolescents and adults. It is based on analysis of over 16,000 subjects who have been vaccinated with at least 1 dose of Trumenba. The most common adverse reactions observed were injection site pain, redness and swelling at the vaccination site, headache, fatigue, chills, diarrhoea, muscle pain, joint pain, and nausea.

7.1. Methods – analysis of data submitted

The primary safety objective for Study B1971060 was to evaluate the safety profile of Trumenba in immunocompromised participants and historical age- and sex-matched healthy participants.

Local reactions (redness, swelling and pain at the site of administration), systemic events (fever [defined as a temperature of ≥38.0°C], vomiting, diarrhoea, headache, fatigue, chills, muscle pain other than muscle pain at the injection site, and joint pain), and use of antipyretic medication were recorded daily in the e-diary for 7 days (Day 1 through Day 7, where Day 1 is the day of vaccination) after each vaccination, and then classified as mild, moderate, or severe. For events that resolved after Day 7, the end date was collected in the case report form (CRF).

Adverse events (AEs; serious and nonserious) were assessed at each study visit and documented on the CRF.

Immediate AEs, defined as AEs occurring within the first 30 minutes after study intervention administration, were assessed and documented on the AE CRF. The time of onset was recorded for any AEs that occurred on the same day as study intervention administration.

Medically attended adverse events (MAEs) and newly diagnosed chronic medical conditions (NDCMCs) were assessed throughout the study and documented on the appropriate AE CRF. An MAE was defined as a nonserious AE that results in an evaluation at a medical facility. An NDCMC was defined as a disease or medical condition, not previously identified, that is expected to be persistent or otherwise long-lasting in its effects.

All safety data were descriptively summarised according to the vaccine received. The safety population was used for the analysis. The safety population was defined as all enrolled participants who received at least 1 dose of the study intervention and have safety data reported after vaccination.

Rapporteur's Assessment

In general, the methods to assess safety are endorsed. They are comparable to the methods used in Study B1971057, which is appropriate.

7.2. Results

Exposure

The safety population is presented in Table 8. All 53 (100.0%) immunocompromised participants enrolled in Study B1971060 received Vaccination 1 compared with 51 (96.2%) healthy controls in Study B1971057. Among enrolled participants in each study, 47 (88.7%) received Vaccination 2 and completed the vaccination phase.

Table 8 Safety Populations

	Vaccine Group (as Administered)	
	Trumenba (B1971060) (N[a]=53)	**Historical Age- and Sex-Matched Controls (Trumenba + Menveo) (B1971057) (N[a]=51)**
	n[b] (%)	**n[b] (%)**
Vaccinated[c]	53	51
Safety population	53 (100.0)	51 (100.0)
Excluded from safety population	0	0
Vaccination 1 safety population	53 (100.0)	51 (100.0)
Excluded from Vaccination 1 safety population	0	0
Vaccination 2 safety population	47 (88.7)	47 (92.2)
Excluded from Vaccination 2 safety population	6 (11.3)	4 (7.8)
Follow-up safety population	44 (83.0)	48 (94.1)
Excluded from follow-up safety population	9 (17.0)	3 (5.9)

Note: The 2 participants in the B1971057 control group were randomised but withdrew before any vaccination.
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. The values in this row were used as the denominators for percentage calculations. This includes participants who received at least 1 dose of investigational product.

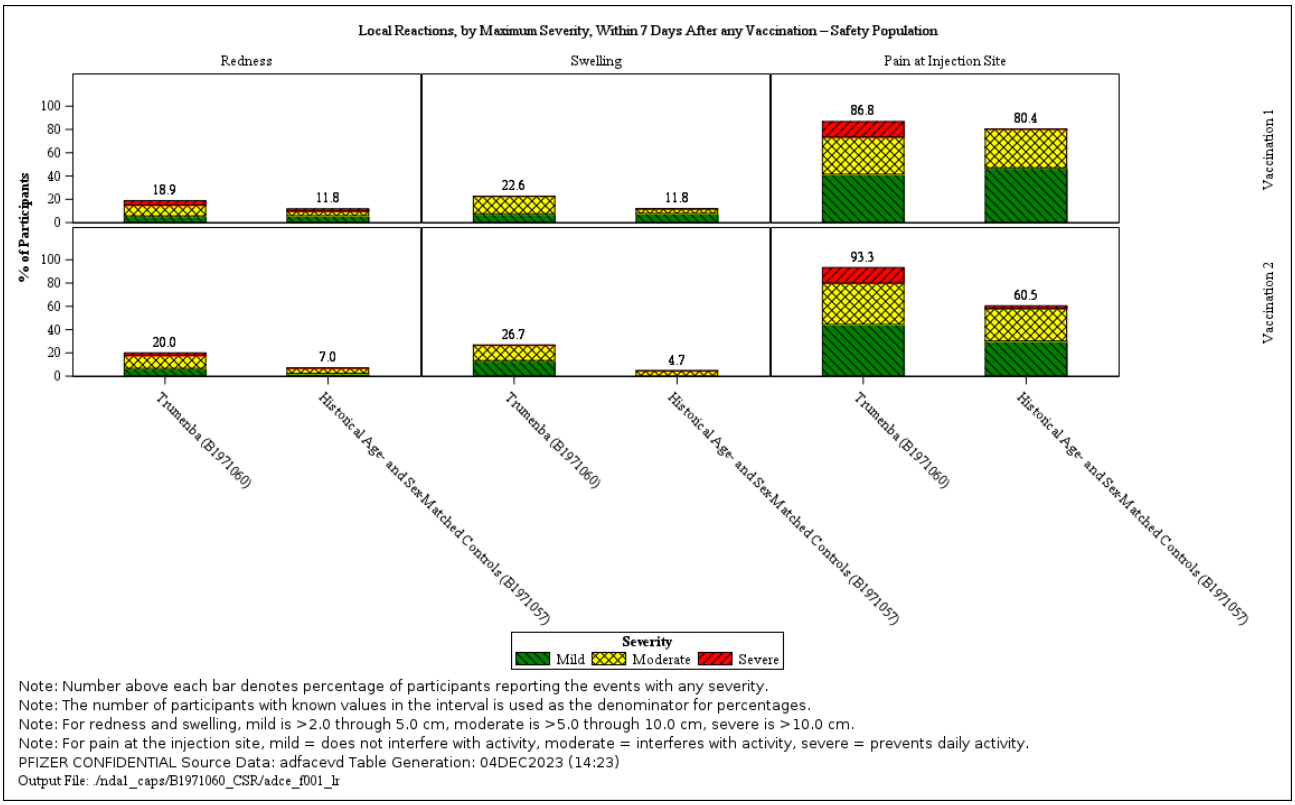
Rapporteur's Assessment

The safety population is limited, with only 53 immunocompromised individuals.

Reactogenicity

Local reactions

Local reactions were reported by 90.6% of immunocompromised participants within 7 days after any vaccination and 88.2% of historical controls. Local reactions (redness, swelling, and pain) at the injection site after Vaccination 1 were reported among 18.9% to 86.8% of immunocompromised participants compared with 11.8% to 80.4% of healthy controls. After Vaccination 2, the corresponding ranges were 20.0% to 93.3% of immunocompromised participants compared with 4.7% to 60.5% of healthy controls (see Figure 3). In both groups, pain at the injection site was the most commonly reported local reaction after any vaccination; most local reactions were mild or moderate in severity. Severe pain at the injection site after any vaccination was reported among 18.9% of immunocompromised participants compared with 2.0% of healthy controls.



Note: Number above each bar denotes percentage of participants reporting the events with any severity.
Note: The number of participants with known values in the interval is used as the denominator for percentages.
Note: For redness and swelling, mild is >2.0 through 5.0 cm, moderate is >5.0 through 10.0 cm, severe is >10.0 cm.
Note: For pain at the injection site, mild = does not interfere with activity, moderate = interferes with activity, severe = prevents daily activity.
PFIZER CONFIDENTIAL Source Data: adfacevd Table Generation: 04DEC2023 (14:23)
Output File: /nda1_caps/B1971060_CSR/adce_f001_lr

Figure 3 Local Reactions, by Maximum Severity, Within 7 Days After Any Vaccination – Safety Population

In both immunocompromised participants and healthy controls, the median onset was 2.0 days for redness and 1.0 day for pain at the injection site after both Vaccination 1 and Vaccination 2. In both groups, the median onset was 1.0 day for swelling after Vaccination 1 and 1.5 days after Vaccination 2.

In immunocompromised participants compared with healthy controls, the median duration was 2.0 days versus 1.0 day for swelling and 3.0 days versus 2.0 days for pain at the injection site, after both Vaccination 1 and Vaccination 2. The median duration of redness was 1.0 day after Vaccination 1 in both groups and 2.0 days after Vaccination 2 in immunocompromised participants versus 1.0 day in healthy controls.

Rapporteur's Assessment

Any local reaction after any vaccination were reported by a comparable number of participants in both the immunocompromise population (90.6%) and the historical controls (88.2%). The reactogenicity profile for local reactions was largely comparable between immunocompromised population and the healthy historical controls, with the most commonly reported local reaction being pain at the injection site and the majority of reactions being mild to moderate in intensity and of short duration (<3 days). However, it should be noted that local reactions seem to occur more frequently in the immunocompromised population with an increased severity, especially after the second vaccination. However, this might be influenced by the open-label design of the current study compared to the observer-blinded study design of study B1971057, although even in that study all participants were aware that they would receive active vaccination. In addition, any strong conclusions on safety profile compared to healthy individuals is hampered by the fact that this entails a cross-study comparison, due to bias inherent in the fact that the studies are conducted in different regions, time and study populations.

Systemic events

Systemic events were reported by 73.6% of immunocompromised participants within 7 days after any vaccination and 70.6% of historical controls. Systemic events (fever, fatigue, headache, chills, vomiting, diarrhoea, muscle pain, and joint pain) after Vaccination 1 were reported among 1.9% to 54.7% of immunocompromised participants compared with 2.0% to 51.0% of healthy controls (Figure 4, Figure 3). After Vaccination 2, the corresponding ranges were 2.2% to 53.3% of immunocompromised participants compared with 0% to 41.9% of healthy controls. Fatigue and headache were the most commonly reported systemic events in both groups. Most systemic events were mild or moderate in severity.

Antipyretic medications to treat fever or pain after Vaccination 1 was reported among 34.0% of immunocompromised participants compared with 9.8% of healthy controls, and decreased after Vaccination 2 (28.9% versus 7.0%, respectively).

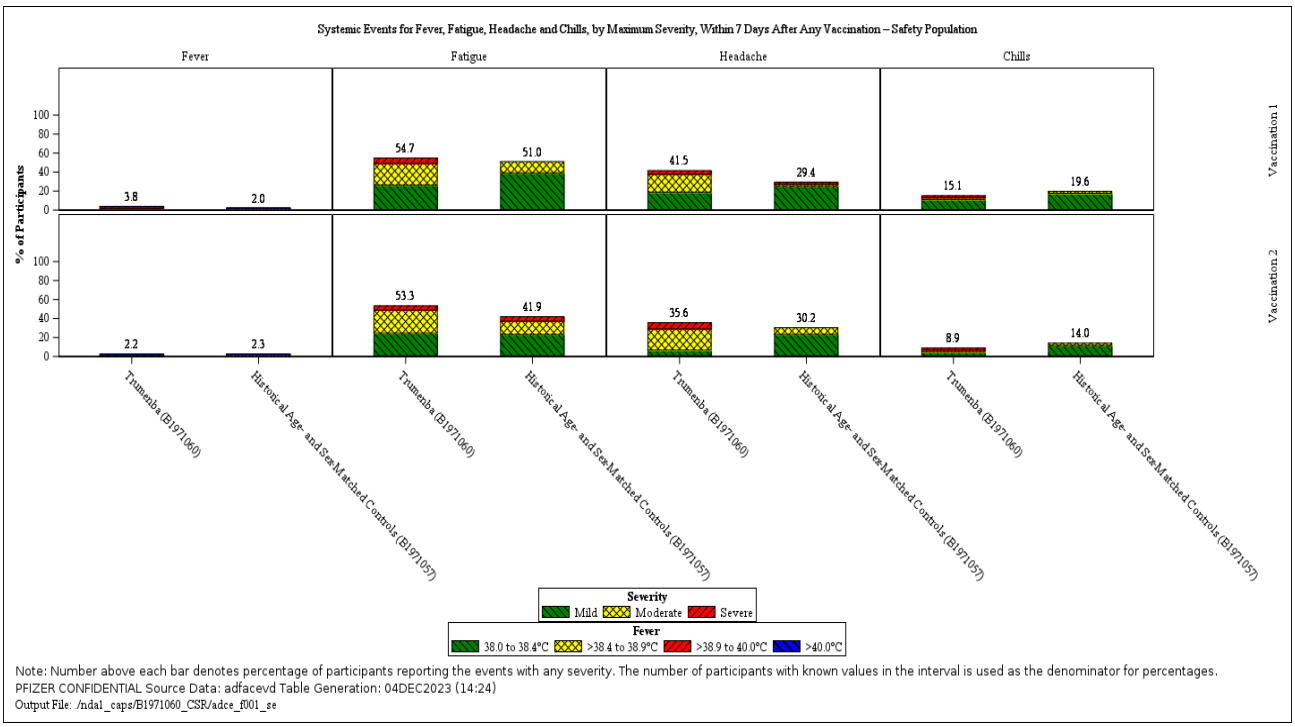


Figure 4 Systemic Reactions of Fever, Fatigue, Headache and Chills, by Maximum Severity, Within 7 Days After Any Vaccination – Safety Population

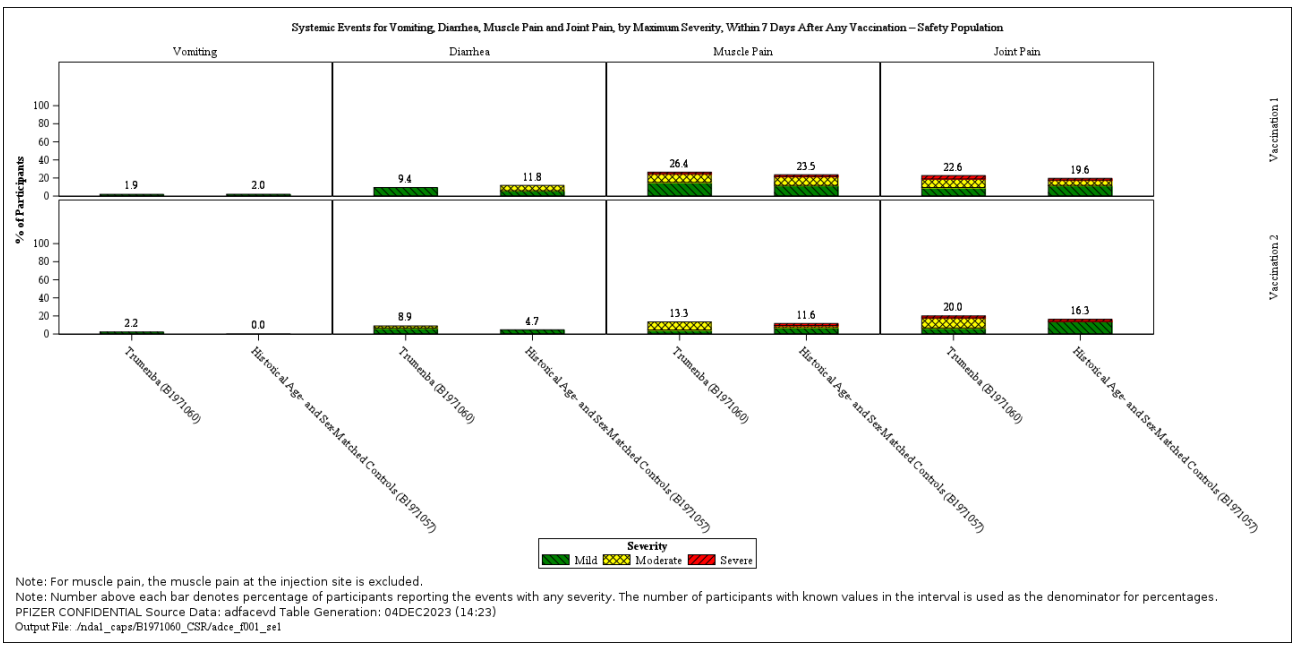


Figure 5 Systemic Reactions of Vomiting, Diarrhoea, Muscle Pain and Joint Pain, by Maximum Severity, Within 7 Days After Any Vaccination – Safety Population

The median day of onset of systemic events after Vaccination 1 ranged from 1.0 to 2.0 days in immunocompromised participants compared with 2.0 to 5.0 days in healthy controls. After Vaccination 2, the median day of onset of systemic events ranged from 1.0 to 2.0 days for both groups, although the median onset of diarrhoea was 3.5 days in immunocompromised participants and 4.5 days in healthy controls.

The median day of onset for the use of antipyretic medications after Vaccinations 1 and 2 in immunocompromised participants were 1.0 day and 2.0 days, respectively and in healthy controls, 2.0 days and 4.0 days, respectively.

After Vaccination 1, the median duration of systemic events ranged from 1.0 to 2.0 days in immunocompromised participants and 1.0 day in healthy controls. After Vaccination 2, the median duration of systemic events ranged from 1.0 to 3.0 days in immunocompromised participants and from 1.0 to 2.0 days in healthy controls.

The median duration of antipyretic medication use after Vaccinations 1 and 2 was 2.0 days in immunocompromised participants and 1.0 day in healthy controls.

Rapporteur's Assessment

Any systemic reaction after any vaccination were reported by a comparable number of participants in both the immunocompromise population (73.6%) and the historical controls (70.6%). The reactogenicity profile for systemic reactions was largely comparable between immunocompromised population and the healthy historical controls, with the most commonly reported systemic reaction being fatigue, followed by headache and muscle pain and the majority of reactions being mild to moderate in intensity and of short duration (<3 days). Overall, a slight increase in the severity of systemic reactions can be observed, with more participants in the immunocompromised population experiencing systemic reactions of moderate severity. However, this might be influenced by the open-label design of the current study compared to the observer-blinded study design of study B1971057, although even in that study all participants were aware that they would receive active vaccination.

More participants in the immunocompromised population reported use of antipyretic medication to treat fever or pain. This might be due to the open-label nature of the study and the fact that these participants are likely to seek medication.

Adverse events

A summary of the frequency of participants reporting at least 1 adverse event for each analysis interval is presented in Table 9.

Table 9 Number (%) of Participants Reporting at Least 1 Adverse Event for Each Analysis Interval – Safety Population

	Vaccine Group (as Administered)							
	Trumenba (B1971060)				Historical Age- and Sex-Matched Controls (Trumenba + Menveo) (B1971057)			
Phase Adverse Event Category	N[a]	n[b] (%)	(95% CI[c])	No. of Events[d]	N[a]	n[b] (%)	(95% CI[c])	No. of Events[d]
Within 30 days after any vaccination								
All AEs	53	18 (34.0)	(21.5, 48.3)	26	51	9 (17.6)	(8.4, 30.9)	17
Related	53	2 (3.8)	(0.5, 13.0)	2	51	3 (5.9)	(1.2, 16.2)	4
Severe	53	3 (5.7)	(1.2, 15.7)	3	51	1 (2.0)	(0.0, 10.4)	1
All SAEs	53	5 (9.4)	(3.1, 20.7)	5	51	0	(0.0, 7.0)	0
Related	53	0	(0.0, 6.7)	0	51	0	(0.0, 7.0)	0
All MAEs	53	16 (30.2)	(18.3, 44.3)	21	51	5 (9.8)	(3.3, 21.4)	6
All NDCMCs	53	1 (1.9)	(0.0, 10.1)	1	51	0	(0.0, 7.0)	0
During the vaccination phase[e]								
All AEs	53	32 (60.4)	(46.0, 73.5)	61	51	21 (41.2)	(27.6, 55.8)	42
Related	53	2 (3.8)	(0.5, 13.0)	2	51	3 (5.9)	(1.2, 16.2)	4
Severe	53	6 (11.3)	(4.3, 23.0)	8	51	2 (3.9)	(0.5, 13.5)	2

All SAEs	53	9 (17.0)	(8.1, 29.8)	13	51	0	(0.0, 7.0)	0
Related	53	0	(0.0, 6.7)	0	51	0	(0.0, 7.0)	0
All MAEs	53	29 (54.7)	(40.4, 68.4)	48	51	15 (29.4)	(17.5, 43.8)	24
All NDCMCs	53	1 (1.9)	(0.0, 10.1)	1	51	0	(0.0, 7.0)	0
During the follow-up phase[f]								
All SAEs	44	2 (4.5)	(0.6, 15.5)	4	48	1 (2.1)	(0.1, 11.1)	1
Related	44	0	(0.0, 8.0)	0	48	0	(0.0, 7.4)	0
All MAEs	44	7 (15.9)	(6.6, 30.1)	7	48	5 (10.4)	(3.5, 22.7)	9
All NDCMCs	44	0	(0.0, 8.0)	0	48	0	(0.0, 7.4)	0
Throughout the study[g]								
All SAEs	53	10 (18.9)	(9.4, 32.0)	17	51	1 (2.0)	(0.0, 10.4)	1
Related	53	0	(0.0, 6.7)	0	51	0	(0.0, 7.0)	0
All MAEs	53	32 (60.4)	(46.0, 73.5)	55	51	16 (31.4)	(19.1, 45.9)	33
All NDCMCs	53	1 (1.9)	(0.0, 10.1)	1	51	0	(0.0, 7.0)	0

Abbreviations: MAE = medically attended adverse event; NDCMC = newly diagnosed chronic medical conditions.
Note: The two participants in B1971057 control group were randomised but withdrew before any vaccination.
a. N = number of participants in the specified group. This value is the denominator for percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the adverse event specified.
c. Exact 2-sided confidence interval (CI), based on the Clopper and Pearson method.
d. The total number of occurrences of the specified event. Participants can be represented more than once. Event counts are the sum of individual occurrences within that category.
e. During the vaccination phase is defined as the time from the first study vaccination (Visit 1) through 1 month after the second study vaccination (Visit 4).
f. During the follow-up phase is defined as the time from 1 month after the second vaccination (Visit 4) through 6 months after the second vaccination (Visit 5).
g. From Vaccination 1 through 6 months after Vaccination 2 is defined as the time from the first study vaccination (Visit 1) through 6 months after the second vaccination (Visit 5).

For both groups, the SOC of Infections and infestations comprised the most frequent AEs, reported in 37.7% of immunocompromised participants and in 25.5% of healthy controls.

Rapporteur's Assessment

During the vaccination phase (defined as time from Visit 1 (first vaccination) through 1 month after the second study vaccination) more AEs were more frequently experienced by the immunocompromised population compared to the historical controls. This is mainly driven by the underlying medical condition and the fact that study B1971060 was performed during the COVID pandemic.

AEs considered potentially related to the study intervention were experienced by a comparable number of participants in both groups.

Both MAEs and SAEs were reported by a higher proportion of participants in the immunocompromised population.

Related AEs

During the vaccination phase, 2 (3.8%) immunocompromised participants each reported 1 related AE after Vaccination 1 and 3 (5.9%) healthy controls reported related AEs (1 participant after Vaccination 1; 2 participants after Vaccination 2). The 2 related AEs reported in immunocompromised participants were vomiting and periorbital swelling.

Rapporteur's Assessment

During the vaccination phase 2 AEs considered to be related to the study vaccination were experienced by participants in the immunocompromised population: 1 case of vomiting (already labelled as common in the SmPC of Trumenba) and 1 case of periorbital swelling. Periorbital swelling is not labelled.

5 days after Vaccination 1, the participant experienced periorbital swelling of both eyelids associated with itching and pain. There was no redness of the eyes or discharge from the eyes. There were no anaphylaxis symptoms such as breathing problems or hives. 3 days later, the event of periorbital swelling was resolved spontaneously.

Considering allergic reactions are already labelled (of which periorbital swelling might be an indication), this single case does not provide sufficient information to draw a clear conclusion on the causal relationship between vaccination with Trumenba and periorbital swelling.

Serious adverse events/deaths/other significant events

Death

One death was reported among immunocompromised participants. The participant aged between 20 to 30 years received Trumenba Vaccination 1 and died 162 days after Vaccination 1 due to cardiac arrest during a vaso-occlusive crisis related to the underlying sickle cell disease. The investigator considered that there was not a reasonable possibility that the cardiac arrest was related to study intervention.

Rapporteur's Assessment

At 162 days after Vaccination 1, the participant experienced a second episode of vaso-occlusive crisis. The participant experienced a cardiac arrest and died in the emergency department during the presentation for vaso-occlusive crisis. The investigator considered that there was not a reasonable possibility that the cardiac arrest was related to study intervention as the most likely cause of death was disease progression, vaso-occlusive crisis, and cardiac arrest. It can be agreed that this event was not related to study vaccination.

Serious adverse events

SAEs were reported among 18.9% of immunocompromised participants compared with 2.0% of healthy controls throughout the study (Table 10). The most commonly reported SAEs were under the SOCs of Blood and lymphatic system disorders and Infections and infestations. All SAEs under the SOC of Blood and lymphatic system disorders were reported in 4 immunocompromised participants with prior history of sickle cell disease causing 8 serious events of vaso-occlusive crisis (PT: Sickle cell anaemia with crisis). Additionally, both SAEs under the SOC of Cardiac disorders were reported in 2 immunocompromised participants: 1 participant that died due to cardiac arrest during a vaso-occlusive crisis related to the underlying sickle cell disease (this is the participant that died) and 1 participant with prior history of splenectomy and type 2 diabetes mellitus that experienced acute myocardial infarction. No related SAEs were reported in either group.

Table 10 Serious Adverse Events Reported Throughout the Study, by System Organ Class and Preferred Term – Safety Population

	Vaccine Group (as Administered)					
	Trumenba (B1971060) (N[a]=53)			Historical Age- and Sex-Matched Controls (Trumenba + Menveo) (B1971057) (N[a]=51)		
System Organ Class Preferred Term	n[b](%)	(95% CI[c])	No. of Events[d]	n[b](%)	(95% CI[c])	No. of Events[d]
Any event	10 (18.9)	(9.4, 32.0)	17	1 (2.0)	(0.0, 10.4)	1
Blood and lymphatic system disorders	**4 (7.5)**	**(2.1, 18.2)**	**8**	**0**	**(0.0, 7.0)**	**0**
Sickle cell anaemia with crisis	4 (7.5)	(2.1, 18.2)	8	0	(0.0, 7.0)	0
Cardiac disorders	**2 (3.8)**	**(0.5, 13.0)**	**2**	**0**	**(0.0, 7.0)**	**0**

Acute myocardial infarction	1 (1.9)	(0.0, 10.1)	1	0	(0.0, 7.0)	0
Cardiac arrest	1 (1.9)	(0.0, 10.1)	1	0	(0.0, 7.0)	0
Gastrointestinal disorders	**1 (1.9)**	**(0.0, 10.1)**	**1**	**0**	**(0.0, 7.0)**	**0**
Pancreatitis chronic	1 (1.9)	(0.0, 10.1)	1	0	(0.0, 7.0)	0
Infections and infestations	**3 (5.7)**	**(1.2, 15.7)**	**3**	**1 (2.0)**	**(0.0, 10.4)**	**1**
COVID-19	2 (3.8)	(0.5, 13.0)	2	0	(0.0, 7.0)	0
Urinary tract infection	1 (1.9)	(0.0, 10.1)	1	0	(0.0, 7.0)	0
Pneumonia	0	(0.0, 6.7)	0	1 (2.0)	(0.0, 10.4)	1
Injury, poisoning and procedural complications	**2 (3.8)**	**(0.5, 13.0)**	**2**	**0**	**(0.0, 7.0)**	**0**
Femoral neck fracture	1 (1.9)	(0.0, 10.1)	1	0	(0.0, 7.0)	0
Wrist fracture	1 (1.9)	(0.0, 10.1)	1	0	(0.0, 7.0)	0
Respiratory, thoracic and mediastinal disorders	**1 (1.9)**	**(0.0, 10.1)**	**1**	**0**	**(0.0, 7.0)**	**0**
Bronchiectasis	1 (1.9)	(0.0, 10.1)	1	0	(0.0, 7.0)	0

Note: MedDRA (v26.0) coding dictionary applied.
Note: The two participants in B1971057 control group were randomized but withdrew before any vaccination.
Note: The vaccination phase is from the first study vaccination (Visit 1) through 1 month after the second study vaccination (Visit 4).
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event. For "Any event," n = number of participants reporting at least 1 occurrence of any adverse event.
c. Exact 2-sided confidence interval (CI), based on the Clopper and Pearson method.
d. The total number of occurrences of the specified event. Participants can be represented more than once. For "Any event," No. of events = the total number of occurrences of all events.

Rapporteur's Assessment

SAEs were reported by ~19% of participants in the immunocompromised population (n=10) after vaccination with Trumenba. This is substantially more compared to the healthy historical controls (n=1, 2.0%), however most likely linked to the underlying disorders. The most commonly reported SAE was sickle cell anaemia with crisis (n=8 events) reported in 4 immunocompromised participants with prior history of sickle cell disease.

None of the SAEs were considered related to Trumenba, which can be agreed based on assessment of time to onset, other possible aetiologies, lack of a plausible biological mechanism and underlying medical conditions.

Discontinuation

During the vaccination phase and follow-up phase, no immunocompromised participant was withdrawn due to an adverse event.

One immunocompromised participant with prior history of sickle cell disease was withdrawn from the study due to death.

Rapporteur's Assessment

No AEs leading to study drug discontinuation were reported in Study B1971060.

7.3. Discussion

In support of the current variation, safety data from Study B1971060 was submitted. Study B1971060 phase 4, open-label, single-arm study conducted to describe the safety, and tolerability, and immunogenicity of Trumenba when administered to immunocompromised participants ⩾10 years of age with asplenia (anatomic or functional) or complement deficiency.

In total, 53 (100%) participants received vaccination 1 and 47 (88.7%) received vaccination 2 and completed the vaccination phase. The safety population is therefore considered limited.

The reactogenicity profile was largely comparable between immunocompromised population and the healthy historical controls, with the most commonly reported reactogenicity events being pain at the injection site, fatigue and headache and the majority of reactions being mild to moderate in intensity and of short duration (<3 days). It should be noted that local reactions seem to occur with a slightly increased frequency and severity in the immunocompromised population, especially after the second vaccination, and for systemic events a slight increase in the severity was observed. This slight increase was not deemed to be clinically relevant and none of the participants discontinued due to a reactogenicity event. In addition, strong conclusions on safety profile compared to healthy individuals cannot be drawn as this entails a cross-study comparison, which is of limited value due to bias inherent in the fact that the studies are conducted in different regions, times (i.e. during the COVID pandemic or prior) and study populations.

During the vaccination phase (defined as time from Visit 1 (first vaccination) through 1 month after the second study vaccination) the proportion of participants experiencing AEs was higher in the immunocompromised population compared to the historical controls. This is mainly driven by the underlying medical condition and the fact that study B1971060 was performed during the COVID pandemic.

AEs considered potentially related to the study intervention were experienced by a low and comparable percentage of participants in both groups. During the vaccination phase 2 AEs considered to be related to the study vaccination were experienced by participants in the immunocompromised population: 1 case of vomiting (already labelled as common in the SmPC of Trumenba) and 1 case of periorbital swelling. Periorbital swelling is not labelled. As allergic reactions are already labelled (of which periorbital swelling might be an indication), this single case does not provide enough information to draw a clear conclusion on the causal relationship between vaccination with Trumenba and periorbital swelling. No new safety signal was observed.

SAEs were reported by ~19% of participants in the immunocompromised population (n=10) after vaccination with Trumenba. This is substantially more compared to the healthy historical controls (n=1, 2.0%), however this is most likely linked to the underlying disorders. The most commonly reported SAE was sickle cell anaemia with crisis (n=8 events) reported in 4 immunocompromised participants with prior history of sickle cell disease. None of the SAEs are considered related to the study intervention, which can be agreed based on assessment of time to onset, other possible aetiologies, lack of a plausible biological mechanism and underlying medical conditions.

One death was reported, which was not considered related to the study intervention. No AEs leading to study drug discontinuation were reported.

Overall, in the immunocompromised population the reactogenicity profile was largely comparable between immunocompromised population and the healthy historical controls. A slight increase in the reactogenicity profile could be observed, however, this increase was not deemed to be clinically relevant. The submitted clinical data did not raise concerns. No new safety signals were observed.

8. Risk management plan

The MAH submitted an updated RMP version v8.0 with this application. The (main) proposed RMP changes were the following:

- To reflect completion of study B1971060 and to propose removal of the Missing Information "Use

in immunocompromised individuals (e.g., individuals with terminal complement deficiency or asplenia)".

Additionally, with this RMP update, the MAH is taking the opportunity to:

- Remove "Vaccine effectiveness" as Missing Information in the Trumenba RMP, as proposed in the Day 96 and Day 106 PRAC Rapporteur RMP Assessment Reports concerning the MenABCWY RMP version 0.1 submitted as part of the ongoing MenABCWY MAA (Procedure Number EMEA/H/C/006165/0000). The PRAC Rapporteur proposed to remove "Vaccine effectiveness" from the Trumenba RMP at a next regulatory opportunity.
- Add the conclusion of the completed study B1971057 in Part IV of the RMP.

Module	Change	PRAC Assessor comment
Part I. Product Overview	Editorial changes to align with SmPC	Accepted
Part II, Module SI – Epidemiology of the Indications and Target Population	Updated with the most recent epidemiology data available.	Accepted
Part II, Module SIII. Clinical Trial Exposure	Updated to DLP 31 March 2024 and to include completed studies B1971057, B1971008, B1971060, C3511001 and C3511002. Specific exposure tables added for study B1971060.	Cumulatively, through 31 March 2024, more than 23,000 subjects have participated in the bivalent rLP2086 clinical development program and in the MenABCWY clinical development program which utilized bivalent rLP2086. C3511001 and C3511002 were MenABCWY clinical studies. Accepted.
Part II, Module SIV. Populations Not Studied in Clinical Trials	Updated to reflect the revised list of Missing Information.	Accepted
Part II, Module SV. Post-Authorisation Experience	Updated to DLP 31 March 2024	The estimated cumulative worldwide unit distribution for bivalent rLP2086 from launch through 31 March 2024 is approximately 8,832,013 doses. The majority of the exposure (84%) occurred in the US. About 1 million doses were distributed in the EU. Accepted.
Part II, Module SVII.	Update of Module SVII.2 to	The MAH considers that the

Module	Change	PRAC Assessor comment
Identified and Potential Risks	reflect the removal of the Missing Information "Use in immunocompromised individuals (e.g., individuals with terminal complement deficiency or asplenia)" and "Vaccine effectiveness" and the rationale for this action.	safety profile of the Trumenba is now sufficiently characterised in immunocompromised individuals, based on the results of study B1971060. Overall the submitted data did not raise concerns. However, the CHMP Rapporteur requested the narratives for all SAEs to enable assessment of relatedness. This needs to be clarified before removal of this topic from the RMP can be agreed. "Vaccine effectiveness" is being removed from the list of safety concerns, following the recommendation during the MenABCWY MAA (Procedure Number EMEA/H/C/006165/0000). This is accepted.
Part II, Module SVIII. Summary of the Safety Concerns	Removal of the Missing Information "Use in immunocompromised individuals (e.g., individuals with terminal complement deficiency or asplenia)" and "Vaccine effectiveness".	Accepted for the removal related to "Vaccine effectiveness". Removal related to "Use in immunocompromised individuals" pending responses to the RSI of the CHMP Rapporteur.
Part III, Pharmacovigilance Plan (including Post Authorisation Safety Studies)	B1971060 moved from planned to completed PV activities. B1971052 and B1971033 removed as completed PV activities. Investigation of bivalent rLP2086 effectiveness removed from planned PV activities.	The text provided in the RMP completed pharmacovigilance activities (B1971060), is based on data provided in the clinical overview and include results from the safety data for immunocompromised participants ≥10 years of age. Accepted
Part IV. Plans for postauthorization efficacy studies	Updated to reflect completion of study B1971057	Accepted

Module	Change	PRAC Assessor comment
Part V. Risk Minimization Measures	Updated to remove the Missing Information "Use in immunocompromised individuals (e.g., individuals with terminal complement deficiency or asplenia)" and "Vaccine effectiveness" and to remove studies B1971060 and Investigation of bivalent rLP2086 effectiveness.	Accepted for the removal related to "Vaccine effectiveness". Removal related to "Use in immunocompromised individuals" pending responses to the RSI of the CHMP Rapporteur.
Part VI. Summary of the Risk Management Plan	Updated to reflect changes made in the other Parts and Modules of the RMP.	Accepted for the removal related to "Vaccine effectiveness". Removal related to "Use in immunocompromised individuals" pending responses to the RSI of the CHMP Rapporteur.
Part VII Annexes to the Risk Management Plan	Annex 2: Study B1971060 moved from ongoing to completed study. Investigation of bivalent rLP2086 effectiveness removed. Annex 3: Study B1971060 removed. Annex 4: Minor changes to EDP FU Questionnaire due to the retirement of the previous one. Annex 5: Study B1971057 removed. Annex 8: Changes to reflect the updated information in the RMP Part I to Part VI.	Accepted

PRAC Rapporteur assessment comment:

The main purpose of this RMP update are:

- To reflect completion of study B1971060 and to propose removal of the Missing Information "Use in immunocompromised individuals (e.g., individuals with terminal complement deficiency or asplenia)".

Additionally, with this RMP update, the MAH is taking the opportunity to:

- Remove "Vaccine effectiveness" as Missing Information in the Trumenba RMP, as proposed in

the Day 96 and Day 106 PRAC Rapporteur RMP Assessment Reports concerning the MenABCWY RMP version 0.1 submitted as part of the ongoing MenABCWY MAA (Procedure Number EMEA/H/C/006165/0000). The PRAC Rapporteur proposed to remove "Vaccine effectiveness" from the Trumenba RMP at a next regulatory opportunity.

- Add the conclusion of the completed study B1971057 in Part IV of the RMP.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 11. Summary of Safety Concerns

Important identified risks	None
Important potential risks	None
Missing Information	Use in co-administration with MMR and pneumococcal vaccines
	~~Use in immunocompromised individuals (eg. individuals with terminal complement deficiency or asplenia)~~
	~~Vaccine effectiveness~~

MMR: measles, mumps, and rubella.

Missing information "Use in immunocompromised individuals"

In study B1971060, 53 participants enrolled, 51 had anatomic or functional asplenia and 2 had complement deficiency. The results were compared to a random selection of historical age and sex-matched healthy controls from study B1971057. The limited safety database only allowed for comparison of the reactogenicity profile. Overall the submitted data did not raise concerns. However, the CHMP Rapporteur requested the narratives for all SAEs to enable assessment of relatedness. This needs to be clarified before removal of "Use in immunocompromised individuals" from the RMP can be agreed.

Missing information "Vaccine effectiveness"

Vaccine effectiveness is removed following the recommendation during the MenABCWY MAA procedure (Procedure Number EMEA/H/C/006165/0000). There, for consistency, it was proposed to remove vaccine effectiveness from the RMP of Trumenba in a next regulatory opportunity. Removal of this topic is accepted. The Applicant is reminded that vaccine effectiveness should be monitored and discussed in the PSUR as per GVP Module VII and GVP Product-Specific Considerations I - Vaccines for prophylaxis against infectious diseases.

8.1. Overall conclusion on the RMP

☒ The changes to the RMP are acceptable.

9. Changes to the Product Information

As a result of this variation, sections 4.4 and 5.1 of the SmPC are being updated to update the warning on immunocompromised individuals and to add immunogenicity data. An editorial update is included in section 4.8 of the SmPC.

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

10. Request for supplementary information

10.1. Other concerns

Clinical aspects

1. The MAH is requested to clarify that there were no relevant differences in the assay conduction, e.g. assay reagents including references used should be identical and the assays should have been performed in the same laboratories using the same SOP for both study B1971060 and B1971057. This information will add to the information regarding the usefulness of this historical control.
2. The MAH is requested to present the immunogenicity results for participants <50 and ≥50 years of age separately for the immunocompromised participants, to determine the impact of age on immunogenicity results in this population.
3. The MAH is requested to provide the narratives for all SAEs reported by participants in the immunocompromised population, to enable assessment of relatedness.
4. The presentation of the results in the SmPC should be altered from text to table format. The table should be similar to the other tables included in the SmPC and removal of text is proposed to ensure the SmPC is short and concise, and duplication of results is not needed.

11. Assessment of the responses to the request for supplementary information

11.1. Other concerns

Clinical aspects

Question 1
The MAH is requested to clarify that there were no relevant differences in the assay conduction, e.g. assay reagents including references used should be identical and the assays should have been performed in the same laboratories using the same SOP for both study B1971060 and B1971057. This information will add to the information regarding the usefulness of this historical control.

Summary of the MAH's response
Testing for studies B1971057 and B1971060 were executed in the High Throughput Clinical Immunoassay & Diagnostics (HCID, previously named High Throughput Clinical Testing) laboratory in Pearl River, NY. Testing for Study B1971057 stage 1, from which data was used as the control for Study B1971060, was executed in 2018-2019 and testing for Study B1971060 was executed in 2023.

All assay reagent lots were replaced between the completion of Study B1971057 stage 1 and the start of testing for Study B1971060 (2019 and 2023, respectively) as would be expected for assays run several years apart. All reagent lots were appropriately qualified in serum bactericidal assay (SBA) and bridged to prior qualified lots, and therefore have no impact on clinical testing results.

Automated liquid handlers, which were in use from the start of assay development in 2010 were replaced at the end of unit lifetimes in 2021. New robot liquid handlers from a different manufacturer were qualified and bridged to older units. Titer readouts between the 2 instruments were similar, ranging from 91.24 to 107.42% bias for each of the 4 primary MenB SBA strains (see Module 5.3.1.4, VR-VTR-10753; VR-VTR-10766). Therefore, replacement of automated liquid handlers had no impact on clinical testing results.

The SBA does not compare unknown samples to a reference to normalize titer readout. SBA titres are relative values. Day-to-day SBA performance is monitored using 2 quality controls (QC) per MenB clinical test strain. Long-term SBA performance is monitored using one panel of sera per test strain with titres across the validated assay range, and panel titres obtained during execution of the B1971060 and B1971057 studies were comparable for all 4 primary MenB test strains demonstrating that SBA performance and readout were similar for these 2 studies.

Assessment of the MAH's response

The MAH provided information regarding the assay conduct. The testing facility is the same for the 2 studies. Although all reagents were replaced, which is to be expected as there is a 4-year gap between studies, reagents were qualified and bridged to prior qualified lots.

The most reassuring information is that long-term SBA performance is monitored using one panel of sera per test strain with titres across the validated assay range. The titres of the panel acquired during performance of the 2 studies were comparable for all 4 primary MenB test strains. This indicates that SBA performance and readout were comparable for these 2 studies.

Conclusion

Issue considered resolved.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

Question 2

The MAH is requested to present the immunogenicity results for participants <50 and ≥50 years of age separately for the immunocompromised participants, to determine the impact of age on immunogenicity results in this population.

Summary of the MAH's response

Immunogenicity results for immunocompromised participants <50 years of age and ≥50 years of age are provided. As an example results of the percentage of participants achieving hSBA titer ≥LLOQ are provided, see Table 12 and Table 13. There were no clinically meaningful differences in immunogenicity between the younger and older age groups for any primary MenB strains in the immunocompromised participants. It should be noted that the results for the specific age groups are based on a limited number of participants, particularly for the older age group (≥50 years of age), as such any numerical differences across age groups should be interpreted with caution.

Table 12: Number (%) of Participants (<50 Years of Age) with hSBA Titer ⩾ LLOQ for Each of the 4 Primary MenB Strains – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)							
	Trumenba (B1971060)				Historical Age- and Sex-Matched Controls (Trumenba + Menveo) (B1971057)			
MenB Strain (Variant) Time Point	N[a]	n[b]	(%)	(95% CI)[c]	N[a]	n[b]	(%)	(95% CI)[c]
PMB80 (A22)								
Before Vaccination 1	35	9	(25.7)	(12.5, 43.3)	33	10	(30.3)	(15.6, 48.7)
1 Month after Vaccination 2	35	26	(74.3)	(56.7, 87.5)	34	32	(94.1)	(80.3, 99.3)
PMB2001 (A56)								
Before Vaccination 1	35	8	(22.9)	(10.4, 40.1)	34	7	(20.6)	(8.7, 37.9)
1 Month after Vaccination 2	35	31	(88.6)	(73.3, 96.8)	35	35	(100.0)	(90.0, 100.0)
PMB2948 (B24)								
Before Vaccination 1	34	0	(0.0)	(0.0, 10.3)	35	7	(20.0)	(8.4, 36.9)
1 Month after Vaccination 2	35	25	(71.4)	(53.7, 85.4)	35	29	(82.9)	(66.4, 93.4)
PMB2707 (B44)								
Before Vaccination 1	35	1	(2.9)	(0.1, 14.9)	35	3	(8.6)	(1.8, 23.1)
1 Month after Vaccination 2	34	28	(82.4)	(65.5, 93.2)	33	30	(90.9)	(75.7, 98.1)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation. MenB = *Neisseria meningitidis* group 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.
PFIZER CONFIDENTIAL Source Data: adva Output
File: ./nda1_caps/B1971060_CHMP_Aug2024/adva_s005_lloq_comb_lt50 Date of Generation: 16SEP2024 (23:03)

Table 13: Number (%) of Participants (⩾ 50 Years of Age) with hSBA Titer ⩾ LLOQ for Each of the 4 Primary MenB Strains – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)							
	Trumenba (B1971060)				Historical Age- and Sex-Matched Controls (Trumenba + Menveo) (B1971057)			
MenB Strain (Variant) Time Point	N[a]	n[b]	(%)	(95% CI)[c]	N[a]	n[b]	(%)	(95% CI)[c]
PMB80 (A22)								
Before Vaccination 1	8	5	(62.5)	(24.5, 91.5)	9	3	(33.3)	(7.5, 70.1)
1 Month after Vaccination 2	9	7	(77.8)	(40.0, 97.2)	9	9	(100.0)	(66.4, 100.0)
PMB2001 (A56)								
Before Vaccination 1	8	3	(37.5)	(8.5, 75.5)	9	3	(33.3)	(7.5, 70.1)
1 Month after Vaccination 2	9	9	(100.0)	(66.4, 100.0)	9	9	(100.0)	(66.4, 100.0)
PMB2948 (B24)								

MenB Strain (Variant) Time Point	Vaccine Group (as Randomized) Trumenba (B1971060) N[a]	n[b]	(%)	(95% CI)[c]	Historical Age- and Sex-Matched Controls (Trumenba + Menveo) (B1971057) N[a]	n[b]	(%)	(95% CI)[c]
Before Vaccination 1	8	1	(12.5)	(0.3, 52.7)	8	3	(37.5)	(8.5, 75.5)
1 Month after Vaccination 2	9	6	(66.7)	(29.9, 92.5)	9	7	(77.8)	(40.0, 97.2)
PMB2707 (B44)								
Before Vaccination 1	8	3	(37.5)	(8.5, 75.5)	9	2	(22.2)	(2.8, 60.0)
1 Month after Vaccination 2	9	6	(66.7)	(29.9, 92.5)	9	9	(100.0)	(66.4, 100.0)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation. MenB = *Neisseria meningitidis* group 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.
PFIZER CONFIDENTIAL Source Data: adva Output
File: ./nda1_caps/B1971060_CHMP_Aug2024/adva_s005_lloq_comb_ge50 Date of Generation: 13SEP2024 (08:38)

Assessment of the MAH's response

The MAH presented all immunogenicity results (% of participants achieving a hSBA Titer ≥ LLOQ, % of participants achieving 4-fold rise and hSBA GMTs) for the immunocompromised participants <50 and ≥50 years of age separately. Based on the results presented, no clear difference could be observed between the participants aged <50 and ≥50 after vaccination. The impact of age was limited. It should be noted that only approximately 9 participants contributed to the ≥50 year of age subgroup.

Conclusion

Issue considered resolved

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

Question 3

The MAH is requested to provide the narratives for all SAEs reported by participants in the immunocompromised population, to enable assessment of relatedness.

Summary of the MAH's response

Throughout Study B1971060, 10 participants reported 17 SAEs, all of which were considered not related to the study intervention.

The B1971060 CSR included narratives for 1 participant reporting 3 SAEs (B1971060 CSR Section 14). Case summaries for the remaining 9 participants reporting 14 SAEs were presented.

Assessment of the MAH's response
All narratives for the SAEs in immunocompromised participants have now been provided, which is appreciated. It can be agreed that none of the SAEs can convincingly be related to the study intervention. The majority of SAEs, except for exacerbation of sickle cell anaemia and COVID-19, occurred in single participants. It can be agreed that none of the SAEs are related to study intervention, based on time to onset, other possible aetiologies of the SAEs, lack of a plausible biological mechanism and underlying medical conditions.

Conclusion

Issue considered resolved.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

Question 4
The presentation of the results in the SmPC should be altered from text to table format. The table should be similar to the other tables included in the SmPC and removal of text is proposed to ensure the SmPC is short and concise, and duplication of results is not needed.

Summary of the MAH's response
The MAH acknowledges the EMA's proposal and has updated the SmPC as suggested. The proportion of subjects with hSBA titres ≥ 1:8 or 16 against the 4 primary test strains after two doses of Trumenba one month after the second vaccination is presented in a tabular format, rather than as text, consistent with the presentation of previous study results in the SmPC.

Assessment of the MAH's response
The changes proposed by the MAH are acceptable.

Conclusion

Issue considered resolved.

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance