22 September 2022
EMA/491873/2023
Committee for Medicinal Products for Human Use (CHMP)

Type II variation assessment report

Trumenba

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

Procedure No. EMEA/H/C/004051/II/0037

Note

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

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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 26 August 2021 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 4.8 and 5.1 of the SmPC in order to include immunopersistence and booster data based on final results from study B1971035 listed as a part of the paediatric investigation plan; this is a phase 2, randomized, controlled, observer-blinded study conducted to describe the immunogenicity, safety, and tolerability of Bivalent rLP2086 when administered to healthy toddlers aged 12 to <18 Months or 18 to <24 months, and the safety and immunogenicity of a booster dose of Bivalent rLP2086.

The requested variation proposed amendments to the Summary of Product Characteristics.

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

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 purpose of this submission is to add information to sections 4.8 and 5.1 of the SmPC concerning immunopersistence and booster data based on final results from study B1971035. In addition, small amendments are made to other parts of SmPC section 5.1, not detailing the persistence or booster information.

Study B1971035 is a phase 2, randomized, controlled, observer-blinded study conducted to describe the immunogenicity, safety, and tolerability of bivalent rLP2086 when administered to healthy toddlers aged 12 to <18 months or 18 to <24 months (Stage 1) and the safety and immunogenicity of a booster dose of bivalent rLP2086 (Stage 2). The current submission includes data from Stage 2 of study B1971035, which assessed the duration of the immune response and the response to a booster dose and fulfils Post Authorisation Measure P46/016.

The persistence of hSBA titres in young children was observed to be poor as 6 months after primary vaccination, the proportion of participants with hSBA titres ≥LLOQ (10.3% (B24) and 59.1% (A56) in the 120 µg rLP2086 group) was reduced substantially compared to 1 month after the primary vaccination series (71.6% to 100% in the 120 µg rLP2086 group). Over time the proportion of participants with hSBA titres ≥LLOQ declined further to 3.7% (A22 and B24) and 22.8% (A56) in the 120 µg rLP2086 group. In line with these results, hSBA titres were reduced to levels only slightly higher than prior to vaccination levels at month 6 after primary vaccination series. A further reduction was observed from 6 months to 24 months after primary vaccination. A booster, received approximately 26 months after vaccination 3 of the

primary vaccination series, was able to induce a strong anamnestic response, with ≥92.6% of participants achieving hSBA titres ≥LLOQ.

Trumenba is a reactogenic vaccine, with the majority of participants reporting local and systemic reactions. Most reactions were mild to moderate in intensity and of short duration (<3 days). No new safety signals were observed either during the persistence analysis period or after the booster dose. The data presented is agreed to be added to the SmPC.

An endorsing comment was received from MS1 during the procedure.

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 and IIIB

Update of sections 4.8 and 5.1 of the SmPC in order to include immunopersistence and booster data based on final results from study B1971035 listed as a part of the paediatric investigation plan; this is a phase 2, randomized, controlled, observer-blinded study conducted to describe the immunogenicity, safety, and tolerability of Bivalent rLP2086 when administered to healthy toddlers aged 12 to <18 months or 18 to <24 months, and the safety and immunogenicity of a booster dose of Bivalent rLP2086.

In addition, the MAH is also taking this opportunity to introduce editorial changes in the SmPC and to update the list of local representatives in the Package Leaflet.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and III 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/004051/II/0037.

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.

With the present submission the MAH intends update sections 4.8 and 5.1 of the SmPC in order to include inmunopersistence and booster data based on final results from study B1971035.

Study B1971035 is a phase 2, randomized, controlled, observer-blinded study conducted to describe the immunogenicity, safety, and tolerability of Bivalent rLP2086 when administered to healthy toddlers aged 12 to <18 Months or 18 to <24 months (Stage 1), and the safety and immunogenicity of a booster dose of Bivalent rLP2086 (Stage 2).

Stage 1 of study B1971035, which evaluates the primary vaccination, has been assessed during procedure EMEA/H/C/004051/II/0013. The current submission includes data from Stage 2 of study B1971035, which assessed the duration of the immune response and the response to a booster dose.

6. Clinical Efficacy aspects

The application is based on the results of study B1971035.

The study design is presented in Figure 1. Stage 2 was open-label.

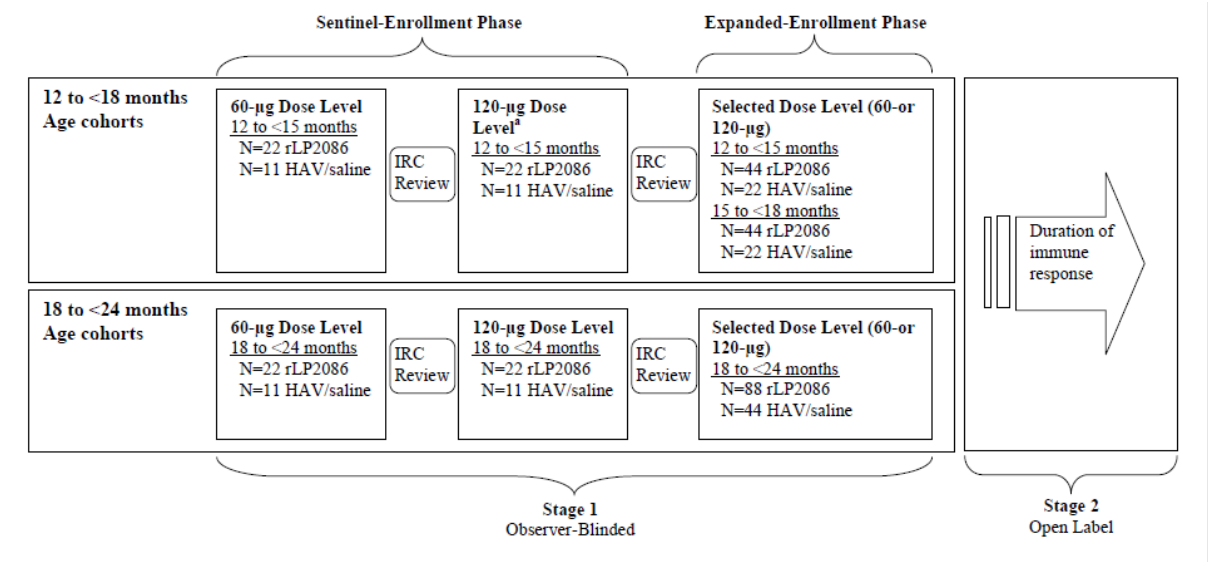


Figure 1 Study design

The second stage of the study, subject of the currently submitted data, was designed to evaluate the duration of the immune response up to approximately 2 years after the third dose of bivalent rLP2086; hence, only those participants randomly assigned to bivalent rLP2086 (irrespective of dose level) were eligible for Stage 2. Stage 2 also described the safety and immunogenicity of a single booster dose of 120 µg of bivalent rLP2086 given approximately 2 years after Vaccination 3 of the primary series. Only

participants who received 3 doses of 120-µg bivalent rLP2086 in Stage 1 were eligible to receive the booster vaccination.

The study was conducted between August 2015 and July 2020 at 26 centres in four countries (Australia, Czech Republic, Finland and Poland) in accordance with GCP. Participants from a total of 16 sites (Australia, Czech Republic, and Poland) received the booster vaccination. Finland was not selected to participate in the booster protocol amendment.

Only data from stage 2 are contained within the current submission.

6.1. Methods – analysis of data submitted

Study participants

Children, male or female, in the ages of 12-<24 months could be enrolled in Stage 2.

Exclusion criteria included previous vaccination with MnB or HAV vaccine, a known or suspected disorder of the immune system that would have prevented an immune response to the vaccine, significant neurological disorders or neuroinflammatory conditions.

Participants who received HAV vaccine/saline during Stage 1 were not eligible to enrol in Stage 2. In addition, only participants who received 3 doses of 120-µg bivalent rLP2086 in Stage 1 were eligible to receive the booster vaccination.

Assessor's comments
In general, the inclusion and exclusion criteria seem appropriate. The population enrolled in the clinical study consists of healthy toddlers.

It is regretted that no information on booster after primary vaccination with 60 µg bivalent rLP2086 will be available. During procedure EMEA/H/C/004051/II/0013, there was no clear difference between the 60 and 120 µg dose, albeit on a very limited data set. It would have been interesting to determine booster response after the lower dose as well, to determine whether a difference could be observed in the anamnestic response after a booster dose.

Treatment

A single booster dose (120 µg) of bivalent rLP2086 was administered as an intramuscular injection into either the deltoid muscle or anterolateral thigh muscle at Visit 12 (approximately 2 years after Vaccination 3) only to participants who received 3 doses of 120 µg of bivalent rLP2086 in Stage 1.

Assessor's comments
Treatment is considered acceptable for the intent of the study.

Objectives

Primary Safety Objective

- To evaluate the safety profile of bivalent rLP2086 compared to a control (hepatitis A virus [HAV] vaccine), as measured by local reactions, systemic events, adverse events (AEs), serious adverse events (SAEs), newly diagnosed chronic medical conditions (NDCMCs), medically attended events (MAEs), and immediate AEs in healthy toddlers 12 to <18 months and 18 to <24 months of age at study entry, and in both age strata combined. Of note, only persistence safety data of 3rd dose of Trumenba and booster dose is included in the current submission.

Secondary Immunogenicity Objectives

- To describe the immune response as measured by hSBA performed with 4 primary MnB strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, measured at 6, 12, and 24 months after Vaccination 3 with bivalent rLP2086, in healthy toddlers aged 12 to <18 and 18 to ≤ 24 months at study entry and in both age strata combined.
- To describe the immune response as measured by hSBA performed with 4 primary MnB strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, measured 1 month after the third vaccination with bivalent rLP2086, immediately before the booster dose of bivalent rLP2086 in Stage 2, and 1 month after the booster dose in both age strata combined.

Secondary safety objectives

- To describe the safety profile of a 120µg booster dose of bivalent rLP2086 as measured by local reactions, systemic events, AEs, SAEs, NDCMCs, MAEs, and immediate AEs in both age strata combined.

Assessor's comments

The immunogenicity objectives assessed the immune response by measuring hSBA for 4 MenB strains. This is considered acceptable.

Persistence data was determined in both age strata, which is appreciated. Evaluation of booster dose will be investigated in the age strata combined as prespecified in the SAP. The reason for only investigating the booster dose in the combined age strata is not fully understood. However, considering the limited number of participants, this is not further pursued.

The safety objectives are considered acceptable.

Outcomes/endpoints

The following endpoint will be applied to results in healthy subjects aged 12 months to <24 months (ie, both age strata combined) at study entry:

- Proportion of subjects with hSBA titres ≥ LLOQ for each of the 4 primary MnB test strains 1 month after the third vaccination with bivalent rLP2086.
- Proportions of subjects with hSBA titres ≥ LLOQ, ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the 4 primary strains 1 month after the third vaccination, before the booster vaccination (Visit 12), and 1 month following booster vaccination (Visit 13).
- hSBA GMTs for each of the 4 MnB primary strains 1 month after the third vaccination, before the booster vaccination (Visit 12), and 1 month following booster vaccination (Visit 13).

The following endpoints will be applied to results in healthy subjects aged 12 to <18 months and 18 to <24 months at study entry, and in both age strata combined:

- Proportions of subjects with hSBA titres ≥ LLOQ for each of the 4 primary MnB test strains 1 month after the second vaccination with bivalent rLP2086 and 6, 12, and 24 months after the third vaccination with bivalent rLP2086.
- Proportions of subjects with hSBA titres ≥ LLOQ, ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the 4 primary MnB strains 1 month after the second vaccination and 1, 6, 12, and 24 months after the third vaccination.
- hSBA GMTs for each of the 4 primary test strains 1 month after the second vaccination and 1, 6, 12, and 24 months after the third vaccination

Due to limitation of the serum sample volume, 2 of the primary strains (PMB80 [A22] and PMB2948 [B24]) were tested at each blood sampling time point for half of the subjects (in both age groups), and the other 2 primary strains (PMB2001 [A56] and PMB2707 [B44]) were tested at each blood sampling time point for the remaining half of the subjects.

Assessor's comments

As endpoints both hSBA GMTs and proportion of participants with hSBA titres ≥ LLOQ, ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 at each applicable blood sampling time point will be determined. An hSBA titer of ≥1:4 is the presumptive correlate of protection.

It is understood that due to limitations of serum volume, 2 strains were tested at each blood sampling period for half of the subjects and the other 2 strains in the other half. During Stage 1 it was mentioned that once testing was complete and enough serum was available the other strains not tested yet would be tested. It is not understood why this is not mentioned for Stage 2.

Sample size

Sample size was not based on hypothesis testing as all planned analyses were descriptive.

Approximately 264 subjects were expected to continue on to Stage 2 and, of these, up to approximately 220 are expected to receive the booster vaccination.

Assessor's comments

As all analyses are descriptive, no sample size calculation is relevant.

Finland was excluded from amendment 3, as only 14 Finish participants remained in the study at the time of amendment 3. As adequate numbers of potential participants to meet the target sample size for the booster vaccination remained in the other countries, the study was descriptive, and the sample size was not driven by hypothesis testing; this explanation is considered sufficient.

Randomization and blinding

Stage 2 was designed to evaluate the duration of the immune response up to approximately 2 years after the third dose of bivalent rLP2086; hence, only those participants randomly assigned to bivalent rLP2086 (irrespective of dose level) were eligible for Stage 2. Stage 2 includes Visit 11 (24 months after Vaccination 3) to Visit 14 (6 months after booster vaccination). Participants who received HAV vaccine/saline during Stage 1 were not eligible for Stage 2.

Stage 2 also described the safety and immunogenicity of a single booster dose of 120 µg of bivalent rLP2086 given approximately 2 years after Vaccination 3 of the primary series. Only participants who received 3 doses of bivalent rLP2086 in Stage 1 at the 120-µg dose level were eligible to receive the booster vaccination.

Stage 2 was unblinded for all study and site personnel. The booster vaccination was administered during Stage 2 in an open-label fashion.

Assessor's comments

Stage 2 is an open-label extension on Stage 1, which is considered acceptable. It is designed to evaluate the duration of the immune response after the third dose of the primary vaccination sequence and safety and immunogenicity of a booster dose, both of which are not considered to be impacted by the open-label design of the study as participant already had received multiple doses of Trumenba.

Statistical methods

There were no statistical hypotheses specified in the protocol. All safety and immunogenicity endpoints were descriptively summarized.

Analysis sets

The evaluable immunogenicity population was the primary population for the immunogenicity analyses and includes all subjects who were randomly assigned to the study group of interest, were eligible, received all investigational products as randomized, had blood drawn for assay testing within the required time frames, had valid and determinate assay results for the proposed analysis, and had no major protocol deviations.

The mITT population includes all randomly assigned subjects who have at least 1 valid and determinate assay result.

The booster evaluable immunogenicity population includes all eligible subjects randomized to 120 µg of bivalent rLP2086 during Stage 1, who received investigational products as randomized including a booster dose, had blood drawn for assay testing within required time frames, had valid and determinate assay results for the proposed analysis, and had no major protocol deviations.

The booster mITT immunogenicity population includes all subjects randomized to 120 µg of bivalent rLP2086 who received the booster dose and who had at least 1 valid and determinate assay result at either Visit 12 (before booster vaccination) or Visit 13 (1 month following booster vaccination).

For persistence endpoints, the safety population includes all subjects who have received at least 1 dose of an investigational product and for whom safety data available. For the safety analysis, subjects were analyzed according to the investigational product received.

For analyses of safety from the time of the booster vaccination and beyond, the booster safety population was used. It includes subjects who have received a booster vaccination and for whom safety data are available.

Immunepersistence analysis

If Visit 11 (24 months after Vaccination 3) was omitted, the pre-booster blood draw at Visit 12 was used to describe persistence of the immune response approximately 2 years after Vaccination 3.

The GMTs and proportions of participants with hSBA titres ≥ LLOQ, ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 were summarized at each blood sampling time point through Month 24 after Vaccination 3 by randomization group for each of the 4 primary strains, along with 2-sided 95% CIs. The empirical RCDCs were presented graphically for each of the 4 primary strains, each group, and each sampling time point through Month 24 after Vaccination 3.

Immune Response to Booster Vaccination

The GMTs and proportions of participants with hSBA titres ≥ LLOQ, ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the 4 MnB primary strains before the booster vaccination (Visit 12) and 1 month following booster vaccination (Visit 13) were summarized with 95% CIs. RCDCs were presented for each of the 4 primary strains for both Visit 12 (before booster vaccination) and Visit 13 (1 month after the booster vaccination).

Missing data

This is not a hypothesis-testing study; thus, an estimation approach will be used to assess the primary, secondary, and exploratory objectives in this study. As assay data are expected to be missing completely at random (MCAR), the primary analysis for the primary objectives were based upon the observed, determinate observations. If all subjects have hSBA tested for all of the 4 primary MnB test strains, descriptive summaries will be provided to describe the reason the hSBA data are missing and the relationship between the missing data indicator and other design variables or covariates (age, race, sex, center, etc) and the observed hSBA data. Additionally, a sensitivity analysis using a mixed-effects model

with repeated measurement (MMRM) will be applied to the primary endpoints. The MMRM uses the maximum likelihood estimation, and it is valid under the assumption that the data are missing at random (MAR).19 If only 50% of the subjects will have 2 strains tested and the remaining 50% have the other 2 strains tested, no sensitivity analyses will be planned because the missing assumption is MCAR.

Log (hSBA) = Group + race + gender + age at randomization +visit+ Group* visit. The intercept will be set as random effect.

In addition to Type III analysis output, least squares GMTs at each visit will be summarized for each strain.

These analyses will only be applied to subjects in the combined age strata in the mITT population, using ½ LLOQ to impute the hSBA values below LLOQ, for the primary strains only.

Assessor's comments
As stated above, it is not understood why booster data are only analysed for both age groups combined. However, considering the limited number of participants, this is not further pursued.

6.2. Results

Participant flow

A summary of the disposition of all randomized participants is presented in Table 1.

Of the participants randomized at entry into Stage 2 (40 [90.9%] and 174 [79.1%] participants in the 60 µg rLP2086 and 120 µg rLP2086 vaccine group, respectively), almost all the participants completed study Visit 11 (24 months after Vaccination 3). Four (9.1%), 63 (28.6%), and 2 (1.5%) participants in the 60 µg rLP2086, 120 µg rLP2086, and HAV/saline vaccine groups respectively were withdrawn after Visit 8 (6 months after Vaccination 3) but before the booster vaccination. As only selected sites implemented the booster vaccination, 14 participants in the 120 µg rLP2086 vaccine group were withdrawn from study as the site did not participate in Stage 2 per Sponsor decision. Additionally, the higher withdrawal rate after Visit 8 (6 months after Vaccination 3) but before the booster vaccination visit (24 months after Vaccination 3) among the 120 µg rLP2086 vaccine group compared to the 60 µg rLP2086 and HAV/saline vaccine groups was due to the fact that the 60 µg rLP2086 and HAV/saline groups completed study participation prior to booster vaccination; the majority of withdrawals in the 120 µg rLP2086 group were due to decision not to participate in the booster amendment portion of the study.

Of the 148 participants who entered the booster stage, 147 participants received the booster dose and completed Stage 2.

No participants were withdrawn due to AEs after Visit 8 (6 months after Vaccination 3) through the end of study.

Table 1 Disposition of subjects

	Vaccine Group (as Randomized)					
	60 µg rLP2086		120 µg rLP2086		HAV/Saline	
	n[a]	(%)	n[a]	(%)	n[a]	(%)
Randomized Stage 1[b]	44		220		132	
Completed Visit 7 (1 month after Vaccination 3)	44	(100.0)	212	(96.4)	129	(97.7)
Completed Visit 8 (6 months after Vaccination 3)	44	(100.0)	210	(95.5)	127	(96.2)
Completed Visit 9 (12 months after Vaccination 3)	42	(95.5)	206	(93.6)	124	(93.9)
Completed Visit 10[c]	42	(95.5)	205	(93.2)	125	(94.7)
Completed Stage 1[d]	42	(95.5)	205	(93.2)	125	(94.7)
Entered Stage 2[e]	40	(90.9)	174	(79.1)	N/A	N/A
Completed Visit 11 (24 months after Vaccination 3)	40	(90.9)	170	(77.3)	N/A	N/A
Withdrawn after Visit 8 but before booster vaccination	4	(9.1)	63	(28.6)	2	(1.5)
Reason for withdrawal after Visit 8 but before booster vaccination						
Lost to follow-up	0	(0.0)	0	(0.0)	1	(0.8)
No longer meets eligibility criteria	1	(2.3)	6	(2.7)	0	(0.0)
No longer willing to participate in study	2	(4.5)	32	(14.5)	1	(0.8)
Other	1	(2.3)	17	(7.7)	0	(0.0)
Withdrew consent	0	(0.0)	8	(3.6)	0	(0.0)
Entered booster stage	N/A		148		N/A	
Received booster vaccination (Visit 12)[f]	N/A		147		N/A	
Booster vaccination phase (Visit 12 through Visit 13)						
Completed	N/A	N/A	147	(100.0)	N/A	N/A
Withdrawn	N/A	N/A	0	(0.0)	N/A	N/A
Booster phase (Visit 12 through Visit 14)						
Completed	N/A	N/A	147	(100.0)	N/A	N/A
Withdrawn	N/A	N/A	0	(0.0)	N/A	N/A
Completed Stage 2	N/A	N/A	147	(100.0)	N/A	N/A

Abbreviation: N/A = not applicable.
Note: The booster vaccination phase is from the booster vaccination (Visit 12) through 1 month after the booster vaccination (Visit 13). The booster phase is from the booster vaccination (Visit 12) through 6 months after the booster vaccination (Visit 14).
a. n = Number of subjects with the specified characteristic.
b. The values in this row are used as the denominators for the percentage calculations through Visit 11.
c. Per study design, Visit 10 can occur at any time between 12 and 24 months post-vaccination 3.
d. Stage 1 is from Visit 1 through Visit 10.
e. Subjects who received HAV/saline during Stage 1 were not eligible for Stage 2.
f. The value in this row is used as the denominator for the percentage calculations for Visit 12 through Visit

Assessor's comments

The proportion of participants who completed Stage 1 was comparable between the treatment groups.

The proportion of participants in the 60 µg dose group entering Stage 2 was higher compared to the proportion of participants in the 120 µg dose group who entered Stage 2, 90.9% vs 79.1%. This is due to the higher proportion of participants no longer willing to participate in the study in the 120 µg dose group compared to the 60 µg dose group, 14.5% vs 4.5%.

In total, 63 participants were withdrawn after Visit 8 but before booster vaccination from the 120µg group according to the disposition of subjects (Table 1). Upon request, the MAH presented information on the 63 participants who were withdrawn after Visit 8 but before booster vaccination in the 120µg group. The immune response appears to be similar between participants who withdrew and participants who continued. There appears to be a slight trend that participants who withdrew experienced slightly more mild to moderate AEs during the vaccination phase compared to participants who continued. This trend is considered not to impact the benefit/risk profile of the product for use as a booster vaccine.

It is reassuring that all participants who entered the booster phase completed Stage 2, and none of the participants withdrew due to an AE.

Recruitment

The first subject was enrolled 31 August 2015 and the last subject last visit was on 17 March 2020. Serology was completed on 07 July 2020.

The study was conducted at 26 sites in Australia, Czech Republic, Finland and Poland. Per the MAH decision sites in Finland did not participate in the booster vaccination part.

Conduct of the study

Protocol amendments

The original protocol dated 16 June 2014 was amended 3 times: 03 February 2015, 19 April 2016 and 18 September 2018.

The protocol was amended (protocol amendment 3) after the primary analysis CSR was finalized. Protocol amendment 3 was implemented only at selected sites. Sites in Finland did not participate in the booster vaccination. The changes implemented were:

- Removal of persistence blood draws at Visits 12 and 13 (36 and 48 months after Vaccination 3, respectively).
- Addition of a prebooster blood draw, a booster dose of 120 µg bivalent rLP2086 in Stage 2, a 1-month postbooster blood draw, and a 6-month postbooster safety telephone contact.
- Addition of wording that protocol amendment 3 will be implemented only at selected sites.
- Updates to language in the Introduction and Biological Samples sections.
- Correction of Fahrenheit equivalent figures for the fever category of 39.0 °C to 39.4°C.

At the time of protocol amendment 3 implementation:

- Participants who received 3 doses of 120 µg of bivalent rLP2086 during Stage 1 who had already completed Visit 11 (24 months after Vaccination 3) and were willing to receive the booster vaccination proceeded to Visit 12 (booster vaccination) as soon as possible within the Visit 12 window to ensure the booster vaccination was received as close to 24 months after Vaccination 3 as possible.
- Participants who received 3 doses of 120 µg of bivalent rLP2086 during Stage 1 who had not already completed Visit 11 and were willing to receive the booster vaccination did not complete Visit 11 and proceeded to Visit 12, preferably at the time Visit 11 was already planned to ensure the booster vaccination was received as close to 24 months after Vaccination 3 as possible.
- Participants who received 120 µg of bivalent rLP2086 during Stage 1 who were not willing to receive the booster vaccination were withdrawn after completion of Visit 11.
- Participants who received 60 µg of bivalent rLP2086 during Stage 1 were withdrawn after completion of Visit 11.

Of the participants that received the booster vaccination almost all participants (96.6%) received the booster vaccination 26 months after Vaccination 3 (1 and 3 participants received the booster vaccination 24 and 25 months after Vaccination 3, respectively).

Assessor's comments

Immune persistence at 36 and 48 months after vaccination 3 were removed to add a booster vaccination in protocol amendment 3. The changes to the study presented in protocol amendment 3 were implemented based on EMA advise. During procedure EMA/H/C/4051/P46, it was observed that immune persistence was poor against 3 of the 4 strains within 6 months of the primary vaccination series in

children aged ≥24 months to 10 years and poorer than has been observed for older individuals ≥10 years of age. It was concluded that post-booster response and persistence studies are therefore warranted among individuals who received their primary series of bivalent rLP2086 as toddlers and children to provide further insights into the utility of a booster dose in providing protection against IMD through childhood, adolescence and early adulthood. The proposed changes to the paediatric investigation plan were approved by the PDCO (EMEA-001037-PIP02-11-M05).

Due to the fact that the protocol was amended while the study was ongoing, participants who received 3 doses of 120 µg of bivalent rLP2086 during Stage 1 could have already completed Visit 11 (24 months after Vaccination 3). In total 143 participants, 96.6%, received the booster vaccination 26 months after vaccination 3, while only 3 received the booster vaccination after 25 months and 1 after 24 months. It is considered that the delay in booster vaccination for the vast majority is not going to affect the immune response.

Protocol deviations

Seven important protocol deviations were reported after Visit 8 (6 months after Vaccination 3) which may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being. The protocol deviations were the following:

- One (1) participant received systemic corticosteroid therapy within 28 days of study vaccination. This participant was excluded from the booster evaluable immunogenicity population based on prespecified SAP criteria 6.
- Six (6) participants with post-booster vaccination (Visit 13) blood samples drawn outside of the protocol-specified time window (28-42 days from the booster vaccination) were excluded from the booster evaluable immunogenicity population based on prespecified SAP criteria 4.

Assessor's comments
All protocol deviations were handled according to the prespecified SAP. This is acceptable.

Baseline data

For the persistence safety population, in the 60 µg rLP2086 vaccine group, 52.5% were female, the majority of participants were white (85%) and non-Hispanic/non-Latino (100%), in the 120 µg rLP2086 vaccine group, 51.8% were female, and the majority of participants were white (95.3%) and non-Hispanic/non-Latino (98.8%). The mean age (SD) at first vaccination was 16.6 (4.17) months in the 60 µg rLP2086 vaccine group and 17.6 (3.60) months in the 120 µg rLP2086 vaccine group, see Table 2.

Table 2 Demographic characteristics – Persistence safety population

	Vaccine Group (as Administered)			
	60 µg rLP2086 (N[a]=40)		120 µg rLP2086 (N[a]=170)	
	n[b]	(%)	n[b]	(%)
Age at first vaccination (months)[c]				
n	40		170	
Mean (SD)	16.6 (4.17)		17.6 (3.60)	
Median	14.0		18.0	
Min, max	12, 23		12, 23	
Sex				
Female	21	(52.5)	88	(51.8)
Male	19	(47.5)	82	(48.2)
Race				
White	34	(85.0)	162	(95.3)
Asian	4	(10.0)	2	(1.2)
Other[d]	2	(5.0)	6	(3.5)
Ethnicity				
Hispanic/Latino	0	(0.0)	2	(1.2)
Non-Hispanic/non-Latino	40	(100.0)	168	(98.8)
Country				
Australia	12	(30.0)	59	(34.7)
Czech Republic	21	(52.5)	36	(21.2)
Poland	7	(17.5)	75	(44.1)

a. N = number of subjects in the specified population. This value was used as the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. Age is determined relative to the randomization date for subjects who were not vaccinated.
d. Other = any race other than white, black, or Asian; however, no black subjects enrolled in the study.

For the booster safety population (120 µg rLP2086 vaccine group), 51.0% were female, the majority of participants were white (94.6%) and non-Hispanic/non-Latino (99.3%). The mean age (SD) at booster vaccination was 54.9 (6.23) months, see Table 3.

Table 3 Demographic characteristics – Booster safety population

	Vaccine Group (as Administered) 120 µg rLP2086 (N[a]=147)	
	n[b]	(%)
Age at booster vaccination (months)[c]		
n	147	
Mean (SD)	54.9 (6.23)	
Median	55.0	
Min, max	43, 67	
Sex		
Female	75	(51.0)
Male	72	(49.0)
Race		
White	139	(94.6)
Asian	2	(1.4)
Other[d]	6	(4.1)
Ethnicity		
Hispanic/Latino	1	(0.7)
Non-Hispanic/non-Latino	146	(99.3)
Country		
Australia	48	(32.7)
Czech Republic	31	(21.1)
Poland	68	(46.3)

a. N = number of subjects in the specified population. This value was used as the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. Age is determined relative to the booster vaccination date for subjects who were vaccinated at Visit 12.
d. Other = any race other than white, black, or Asian; however, no black subjects enrolled in the study.

Assessor's comments

Participants in Finland are not included in the persistence safety population as they did not contribute data at Visit 11.

Numbers analysed

The number of participants included in each of the immunogenicity analysis populations is presented in Table 4.

Table 4 Immunogenicity populations

	Vaccine Group (as Randomized)					
	60 µg rLP2086		120 µg rLP2086		HAV/Saline	
	n[a]	(%)	n[a]	(%)	n[a]	(%)
Randomized[b]	44		220		132	
mITT population	44	(100.0)	220	(100.0)	132	(100.0)
Excluded from mITT population	0	(0.0)	0	(0.0)	0	(0.0)
Evaluable immunogenicity population	40	(90.9)	193	(87.7)	115	(87.1)
Excluded from evaluable immunogenicity population[c]	4	(9.1)	27	(12.3)	17	(12.9)
Not eligible or became ineligible for the study before or at the 1 month post–Vaccination 3 visit	1	(2.3)	8	(3.6)	4	(3.0)
Did not receive all vaccines as randomized at all vaccination visits	0	(0.0)	8	(3.6)	3	(2.3)
Did not have scheduled prevaccination or postvaccination blood drawn[d]	0	(0.0)	21	(9.5)	10	(7.6)
Received prohibited vaccines or treatment	3	(6.8)	6	(2.7)	7	(5.3)
Entered Stage 2[e]	40		174		N/A	
Received booster vaccination[f]	N/A		147		N/A	
Booster mITT immunogenicity population	N/A	N/A	146	(99.3)	N/A	N/A
Excluded from booster mITT immunogenicity population	N/A	N/A	1	(0.7)	N/A	N/A
Booster evaluable immunogenicity population	N/A	N/A	139	(94.6)	N/A	N/A
Excluded from booster evaluable immunogenicity population[c]	N/A	N/A	8	(5.4)	N/A	N/A
Did not have prevaccination blood draw prior to booster vaccination or have postbooster vaccination blood draw[g]	N/A	N/A	7	(4.8)	N/A	N/A
Did not have a valid and determinate assay result at prebooster vaccination visit or postbooster vaccination blood draw visit	N/A	N/A	1	(0.7)	N/A	N/A
Received prohibited vaccines or treatment	N/A	N/A	1	(0.7)	N/A	N/A

Abbreviation: N/A = not applicable.
Note: The mITT population and evaluable immunogenicity population are from Stage 1.
a. n = Number of subjects with the specified characteristic.
b. The values were used as the denominator for the percentage calculations for the mITT and evaluable immunogenicity populations.
c. Subjects may be excluded for multiple reasons.
d. The scheduled post–Vaccination 3 blood draw was 28-42 days after Vaccination 3.
e. Entered Stage 2 values is based on subject completion of Stage 2 informed consent, Visit 11 (24 months after Vaccination 3) or Visit 12 (Pre-booster vaccination).
f. The values were used as the denominator for the percentage calculations for the booster section.
g. The scheduled postbooster vaccination blood draw was 28 to 42 days after the booster vaccination.

Assessor's comments

The proportion of participants excluded from the evaluable immunogenicity population for persistence was comparable between the treatment groups: 9.1% in the 60µg rLP2086 group, 12.3% in the 120 µg rLP2086 group and 12.9% in the HAV/saline group. The most common reason for exclusion from the evaluable immunogenicity population differed: in the 120 µg rLP2086 and HAV/saline group the most common reason was participant did not have scheduled prevaccination or postvaccination blood draw, while in the 60µg rLP2086 group it was participant received prohibited vaccines.

The most common reason for exclusion from the booster evaluable immunogenicity population was comparable to the persistence evaluable immunogenicity population: participant did not have scheduled prevaccination or postvaccination blood draw.

Outcomes and estimation

Proportion of Subjects Achieving an hSBA Titer ≥ LLOQ

The proportions of participants in each age stratum at study entry achieving an hSBA titer ≥ LLOQ from before Vaccination 1 to 24 months after Vaccination 3 for each of the 4 primary MnB test strains is presented in Table 5 for the evaluable immunogenicity population.

Table 5 Subjects With hSBA Titer ≥ LLOQ for Primary Strains – Persistence Analysis

	Vaccine Group (as Randomized)											
	60 µg rLP2086				120 µg rLP2086				HAV/Saline			
Strain (Variant) Sampling Time Point Age Strata	N[a]	n[b]	(%)	(95% CI)[c]	N[a]	n[b]	(%)	(95% CI)[c]	N[a]	n[b]	(%)	(95% CI)[c]
PMB80 (A22)												
Before Vaccination 1												
12 to <24 Months	20	0	(0.0)	(0.0, 16.8)	97	3	(3.1)	(0.6, 8.8)	61	1	(1.6)	(0.0, 8.8)
12 to <18 Months	9	0	(0.0)	(0.0, 33.6)	46	1	(2.2)	(0.1, 11.5)	31	0	(0.0)	(0.0, 11.2)
18 to <24 Months	11	0	(0.0)	(0.0, 28.5)	51	2	(3.9)	(0.5, 13.5)	30	1	(3.3)	(0.1, 17.2)
1 Month after Vaccination 3												
12 to <24 Months	20	18	(90.0)	(68.3, 98.8)	96	86	(89.6)	(81.7, 94.9)	60	3	(5.0)	(1.0, 13.9)
12 to <18 Months	9	8	(88.9)	(51.8, 99.7)	45	41	(91.1)	(78.8, 97.5)	31	1	(3.2)	(0.1, 16.7)
18 to <24 Months	11	10	(90.9)	(58.7, 99.8)	51	45	(88.2)	(76.1, 95.6)	29	2	(6.9)	(0.8, 22.8)
6 Months after Vaccination 3												
12 to <24 Months	20	2	(10.0)	(1.2, 31.7)	97	12	(12.4)	(6.6, 20.6)	58	2	(3.4)	(0.4, 11.9)
12 to <18 Months	10	2	(20.0)	(2.5, 55.6)	46	8	(17.4)	(7.8, 31.4)	30	0	(0.0)	(0.0, 11.6)
18 to <24 Months	10	0	(0.0)	(0.0, 30.8)	51	4	(7.8)	(2.2, 18.9)	28	2	(7.1)	(0.9, 23.5)
12 Months after Vaccination 3												
12 to <24 Months	21	3	(14.3)	(3.0, 36.3)	95	6	(6.3)	(2.4, 13.2)	55	1	(1.8)	(0.0, 9.7)
12 to <18 Months	10	1	(10.0)	(0.3, 44.5)	45	4	(8.9)	(2.5, 21.2)	27	1	(3.7)	(0.1, 19.0)
18 to <24 Months	11	2	(18.2)	(2.3, 51.8)	50	2	(4.0)	(0.5, 13.7)	28	0	(0.0)	(0.0, 12.3)
24 Months after Vaccination 3												
12 to <24 Months	19	0	(0.0)	(0.0, 17.6)	81	3	(3.7)	(0.8, 10.4)	N/A	N/A	N/A	N/A
12 to <18 Months	10	0	(0.0)	(0.0, 30.8)	34	2	(5.9)	(0.7, 19.7)	N/A	N/A	N/A	N/A
18 to <24 Months	9	0	(0.0)	(0.0, 33.6)	47	1	(2.1)	(0.1, 11.3)	N/A	N/A	N/A	N/A
PMB2001 (A56)												
Before Vaccination 1												
12 to <24 Months	19	0	(0.0)	(0.0, 17.6)	95	1	(1.1)	(0.0, 5.7)	53	0	(0.0)	(0.0, 6.7)
12 to <18 Months	9	0	(0.0)	(0.0, 33.6)	46	0	(0.0)	(0.0, 7.7)	24	0	(0.0)	(0.0, 14.2)
18 to <24 Months	10	0	(0.0)	(0.0, 30.8)	49	1	(2.0)	(0.1, 10.9)	29	0	(0.0)	(0.0, 11.9)
1 Month after Vaccination 3												
12 to <24 Months	19	19	(100.0)	(82.4, 100.0)	95	95	(100.0)	(96.2, 100.0)	54	1	(1.9)	(0.0, 9.9)
12 to <18 Months	9	9	(100.0)	(66.4, 100.0)	47	47	(100.0)	(92.5, 100.0)	24	0	(0.0)	(0.0, 14.2)
18 to <24 Months	10	10	(100.0)	(69.2, 100.0)	48	48	(100.0)	(92.6, 100.0)	30	1	(3.3)	(0.1, 17.2)
6 Months after Vaccination 3												
12 to <24 Months	18	11	(61.1)	(35.7, 82.7)	88	52	(59.1)	(48.1, 69.5)	52	2	(3.8)	(0.5, 13.2)
12 to <18 Months	8	3	(37.5)	(8.5, 75.5)	41	25	(61.0)	(44.5, 75.8)	24	1	(4.2)	(0.1, 21.1)
18 to <24 Months	10	8	(80.0)	(44.4, 97.5)	47	27	(57.4)	(42.2, 71.7)	28	1	(3.6)	(0.1, 18.3)
12 Months after Vaccination 3												
12 to <24 Months	16	9	(56.3)	(29.9, 80.2)	93	36	(38.7)	(28.8, 49.4)	53	3	(5.7)	(1.2, 15.7)
12 to <18 Months	9	3	(33.3)	(7.5, 70.1)	45	18	(40.0)	(25.7, 55.7)	23	0	(0.0)	(0.0, 14.8)
18 to <24 Months	7	6	(85.7)	(42.1, 99.6)	48	18	(37.5)	(24.0, 52.6)	30	3	(10.0)	(2.1, 26.5)
24 Months after Vaccination 3												
12 to <24 Months	17	7	(41.2)	(18.4, 67.1)	79	18	(22.8)	(14.1, 33.6)	N/A	N/A	N/A	N/A
12 to <18 Months	9	1	(11.1)	(0.3, 48.2)	39	6	(15.4)	(5.9, 30.5)	N/A	N/A	N/A	N/A
18 to <24 Months	8	6	(75.0)	(34.9, 96.8)	40	12	(30.0)	(16.6, 46.5)	N/A	N/A	N/A	N/A

Strain (Variant) Sampling Time Point Age Strata	Vaccine Group (as Randomized) 60 µg rLP2086 Na	nb	(%)	(95% CI)c	120 µg rLP2086 Na	nb	(%)	(95% CI)c	HAV/Saline Na	nb	(%)	(95% CI)c
PMB2948 (B24)												
Before Vaccination 1												
12 to <24 Months	21	1	(4.8)	(0.1, 23.8)	97	2	(2.1)	(0.3, 7.3)	61	1	(1.6)	(0.0, 8.8)
12 to <18 Months	10	0	(0.0)	(0.0, 30.8)	46	1	(2.2)	(0.1, 11.5)	31	0	(0.0)	(0.0, 11.2)
18 to <24 Months	11	1	(9.1)	(0.2, 41.3)	51	1	(2.0)	(0.0, 10.4)	30	1	(3.3)	(0.1, 17.2)
1 Month after Vaccination 3												
12 to <24 Months	20	17	(85.0)	(62.1, 96.8)	95	68	(71.6)	(61.4, 80.4)	60	3	(5.0)	(1.0, 13.9)
12 to <18 Months	9	8	(88.9)	(51.8, 99.7)	45	32	(71.1)	(55.7, 83.6)	31	1	(3.2)	(0.1, 16.7)
18 to <24 Months	11	9	(81.8)	(48.2, 97.7)	50	36	(72.0)	(57.5, 83.8)	29	2	(6.9)	(0.8, 22.8)
6 Months after Vaccination 3												
12 to <24 Months	20	3	(15.0)	(3.2, 37.9)	97	10	(10.3)	(5.1, 18.1)	58	2	(3.4)	(0.4, 11.9)
12 to <18 Months	10	2	(20.0)	(2.5, 55.6)	46	4	(8.7)	(2.4, 20.8)	30	1	(3.3)	(0.1, 17.2)
18 to <24 Months	10	1	(10.0)	(0.3, 44.5)	51	6	(11.8)	(4.4, 23.9)	28	1	(3.6)	(0.1, 18.3)
12 Months after Vaccination 3												
12 to <24 Months	21	2	(9.5)	(1.2, 30.4)	93	3	(3.2)	(0.7, 9.1)	55	2	(3.6)	(0.4, 12.5)
12 to <18 Months	10	0	(0.0)	(0.0, 30.8)	44	1	(2.3)	(0.1, 12.0)	27	0	(0.0)	(0.0, 12.8)
18 to <24 Months	11	2	(18.2)	(2.3, 51.8)	49	2	(4.1)	(0.5, 14.0)	28	2	(7.1)	(0.9, 23.5)
24 Months after Vaccination 3												
12 to <24 Months	19	1	(5.3)	(0.1, 26.0)	82	3	(3.7)	(0.8, 10.3)	N/A	N/A	N/A	N/A
12 to <18 Months	10	0	(0.0)	(0.0, 30.8)	34	3	(8.8)	(1.9, 23.7)	N/A	N/A	N/A	N/A
18 to <24 Months	9	1	(11.1)	(0.3, 48.2)	48	0	(0.0)	(0.0, 7.4)	N/A	N/A	N/A	N/A
PMB2707 (B44)												
Before Vaccination 1												
12 to <24 Months	19	0	(0.0)	(0.0, 17.6)	95	1	(1.1)	(0.0, 5.7)	54	0	(0.0)	(0.0, 6.6)
12 to <18 Months	9	0	(0.0)	(0.0, 33.6)	46	1	(2.2)	(0.1, 11.5)	24	0	(0.0)	(0.0, 14.2)
18 to <24 Months	10	0	(0.0)	(0.0, 30.8)	49	0	(0.0)	(0.0, 7.3)	30	0	(0.0)	(0.0, 11.6)
1 Month after Vaccination 3												
12 to <24 Months	19	17	(89.5)	(66.9, 98.7)	94	81	(86.2)	(77.5, 92.4)	54	0	(0.0)	(0.0, 6.6)
12 to <18 Months	9	8	(88.9)	(51.8, 99.7)	47	41	(87.2)	(74.3, 95.2)	24	0	(0.0)	(0.0, 14.2)
18 to <24 Months	10	9	(90.0)	(55.5, 99.7)	47	40	(85.1)	(71.7, 93.8)	30	0	(0.0)	(0.0, 11.6)
6 Months after Vaccination 3												
12 to <24 Months	16	4	(25.0)	(7.3, 52.4)	89	36	(40.4)	(30.2, 51.4)	53	1	(1.9)	(0.0, 10.1)
12 to <18 Months	8	1	(12.5)	(0.3, 52.7)	43	17	(39.5)	(25.0, 55.6)	24	1	(4.2)	(0.1, 21.1)
18 to <24 Months	8	3	(37.5)	(8.5, 75.5)	46	19	(41.3)	(27.0, 56.8)	29	0	(0.0)	(0.0, 11.9)
12 Months after Vaccination 3												
12 to <24 Months	16	2	(12.5)	(1.6, 38.3)	90	16	(17.8)	(10.5, 27.3)	51	1	(2.0)	(0.0, 10.4)
12 to <18 Months	9	1	(11.1)	(0.3, 48.2)	43	8	(18.6)	(8.4, 33.4)	22	0	(0.0)	(0.0, 15.4)
18 to <24 Months	7	1	(14.3)	(0.4, 57.9)	47	8	(17.0)	(7.6, 30.8)	29	1	(3.4)	(0.1, 17.8)
24 Months after Vaccination 3												
12 to <24 Months	17	2	(11.8)	(1.5, 36.4)	80	10	(12.5)	(6.2, 21.8)	N/A	N/A	N/A	N/A
12 to <18 Months	9	0	(0.0)	(0.0, 33.6)	39	5	(12.8)	(4.3, 27.4)	N/A	N/A	N/A	N/A
18 to <24 Months	8	2	(25.0)	(3.2, 65.1)	41	5	(12.2)	(4.1, 26.2)	N/A	N/A	N/A	N/A

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; N/A = not applicable.
Note: LLOQ = 1:16 for A22; 1:8 for A56, B24, and B44.
Note: Serology data from 'pre-vaccination' (baseline) and for '1 month after Vaccination 3' are from the Stage 1 testing campaign.
a. N = number of subjects with valid and determinate hSBA titers for the given strain.
b. n = Number of subjects 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 subjects, using the Clopper and Pearson method.

Results for the mITT population were similar to those of the evaluable immunogenicity population.

Subgroup analyses of the proportion of subjects achieving an hSBA titre ≥ LLOQ for each of the 4 primary MnB test strains are presented for the evaluable immunogenicity population by sex and country. There were no clinically important differences observed in the subgroup analyses performed.

Assessor's comments

Persistence of the hSBA response in children aged 12 to 24 months after 3 doses against all of the 4 primary test strains is considered poor, as proportion of participants with hSBA titres ≥LLOQ reduced substantially from 1 month after primary vaccination to 6 months after primary vaccination. A further reduction was observed from 6 months to 24 months after primary vaccination.

One month after three doses against all four primary test strains between 70% and 100% of subjects achieving titres > LLOQ in both treatment groups. After six months, the proportion of participants achieving titres ≥LLOQ reduced substantially and ranged from 10.3% (B24) and 59.1% (A56) in the 120 µg rLP2086 group and 10.0% (A22) to 61.1% (A56) in the 60µg rLP2086 group. At 12 and 24 months after primary vaccination series, the proportion of participants achieving titres ≥LLOQ reduced further. The proportion ranged from 3.2% (B24) and 38.7% (A56) in the 120 µg rLP2086 group and 9.5% (B24) to 56.3% (A56) in the 60µg rLP2086 group at 12 months and 3.7% (A22 and B24) and 22.8% (A56) in the 120 µg rLP2086 group and 0.0% (A22) to 41.2% (A56) in the 60µg rLP2086 group at 24 months.

No clear trends in differences in immune persistence were observed between the age groups in the 120 µg rLP2086 group. In general, no differences of >10% in the proportion of participants achieving hSBA titres ≥LLOQ were observed between the 2 age subgroups. In the 60 µg rLP2086 group, more substantial differences were observed, however this is considered to be due to the small number of participants in the 2 age groups.

hSBA GMTs

The hSBA GMTs in children aged 12 to ≤24 months of age from before Vaccination 1 to 24 months after Vaccination 3 for each of the 4 primary MnB test strains is presented in Table 6 for the evaluable immunogenicity population.

Table 6 hSBA GMTS for primary strains – Evaluable immunogenicity population

Strain / **Time point**	**60 µg rLP2086**			**120 µg rLP2086**			**HAV/saline**		
	N	**GMT**	**(95% CI)**	**N**	**GMT**	**(95% CI)**	**N**	**GMT**	**(95% CI)**
PMB80 (A22)									
Before Vaccination 1	20	8.0	(NE, NE)	97	8.4	(7.9, 9.0)	61	8.1	(7.9, 8.3)
1 Mo after Vaccination 3	20	81.6	(46.6, 142.8)	96	67.3	(53.7, 84.3)	60	8.6	(7.9, 9.3)
6 Mo after Vaccination 3	20	9.2	(7.3, 11.5)	97	9.8	(8.7, 11.1)	58	8.4	(7.8, 9.0)
12 Mo after Vaccination 3	21	9.1	(7.8, 10.7)	95	8.7	(8.1, 9.4)	55	8.1	(7.9, 8.3)
24 Mo after Vaccination 3	19	8.0	(NE, NE)	81	8.6	(7.9, 9.3)	N/A	N/A	N/A
PMB2001 (A56)									
Before Vaccination 1	19	4.0	(NE, NE)	95	4.1	(3.9, 4.3)	53	4.0	(NE, NE)
1 Mo after Vaccination 3	19	142.8	(85.5, 238.6)	95	171.4	(141.6, 207.4)	54	4.2	(3.8, 4.5)
6 Mo after Vaccination 3	18	15.4	(8.1, 29.3)	88	13.0	(10.1, 16.9)	52	4.4	(3.7, 5.2)
12 Mo after Vaccination 3	16	16.0	(7.6, 33.5)	93	8.0	(6.5, 9.9)	53	4.7	(3.9, 5.6)
24 Mo after Vaccination 3	17	10.2	(5.1, 20.6)	79	6.1	(4.9, 7.6)	N/A	N/A	N/A
PMB2948 (B24)									
Before Vaccination 1	21	4.4	(3.6, 5.4)	97	4.1	(4.0, 4.3)	61	4.2	(3.8, 4.6)
1 Mo after Vaccination 3	20	18.4	(11.8, 28.6)	95	15.1	(12.3, 18.6)	60	4.3	(3.9, 4.8)
6 Mo after Vaccination 3	20	4.8	(3.9, 5.9)	97	4.7	(4.2, 5.2)	58	4.2	(3.9, 4.5)
12 Mo after Vaccination 3	21	4.6	(3.8, 5.5)	93	4.2	(3.9, 4.5)	55	4.3	(3.9, 4.8)
24 Mo after Vaccination 3	19	4.6	(3.4, 6.3)	82	4.4	(3.9, 4.8)	N/A	N/A	N/A
PMB2707 (B44)									
Before Vaccination 1	19	4.0	(NE, NE)	95	4.0	(4.0, 4.1)	54	4.0	(NE, NE)
1 Mo after Vaccination 3	19	32.0	(18.3, 55.8)	94	45.6	(35.2, 59.0)	54	4.0	(NE, NE)
6 Mo after Vaccination 3	16	6.4	(3.6, 11.5)	89	7.6	(6.3, 9.1)	53	4.1	(3.9, 4.2)
12 Mo after Vaccination 3	16	4.6	(3.7, 5.6)	90	5.2	(4.5, 5.9)	51	4.1	(3.9, 4.2)
24 Mo after Vaccination 3	17	4.5	(3.7, 5.5)	80	4.9	(4.2, 5.6)	N/A	N/A	N/A

Abbreviations: GMT = geometric mean titer; hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; N/A = not applicable; NE = not estimable.
Note: LLOQ = 1:16 for A22; 1:8 for A56, B24, and B44. Titres below the LLOQ were set to 0.5 × LLOQ for analysis.
Note: Serology data from 'pre-vaccination' (baseline) and for '1 month after Vaccination 3' are from the Stage 1 testing campaign.

a. N = number of subjects with valid and determinate hSBA titres for the given strain.

b. GMTs were calculated using all subjects 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).

Results for the mITT population were similar to those of the evaluable immunogenicity population.

Subgroup analyses of the hSBA GMTs for each of the 4 primary MnB test strains were presented for the evaluable immunogenicity population by sex and country. There were no clinically important differences observed in the subgroup analyses performed.

For each group, the percentages for PMB2001 (A56) and PMB2707 (B44) are based on approximately half the participants (those who had the PMB2001 [A56] and PMB2707 [B44] primary strains tested). Likewise, the percentages for PMB80 (A22) and PMB2948 B24) are based on approximately half the participants (those who had the PMB80 [A22] and PMB2948 [B24] primary strains tested). Data was missing for the fewest participants at baseline (≤2 participants for all reasons and groups) and the most participants at 24 month after Vaccination 3 (≤24 participants for all reasons and groups). The majority of missing results were due to withdrawal from the study.

Assessor's comments

The results of the hSBA GMTs are in line with the proportion of participants achieving hSBA titres ≥LLOQ. Again persistence of the hSBA response in children aged 12 to 24 months after 3 doses against all of the 4 primary test strains is considered poor. The hSBA GMTs decreased substantially from 1 month after primary vaccination to 6 months after primary vaccination, reducing hSBA GMTs to levels only slightly higher than prior to vaccination levels. Where levels at 6 months after primary vaccination were still slightly higher compared to prevaccination titres, a further reduction was observed from 6 months to 24 months after primary vaccination.

No clear trends were observed for the 2 age groups, sex or country.

As stated in the protocol, 2 strains were tested at each blood sampling period for half of the subjects and the other 2 strains in the other half. Missing data was limited before vaccination 1 and mainly due to the fact that the results of the assay were indeterminate. From 1 month after vaccination 3, the main reason for missing data was withdrawal from the study.

Reverse Cumulative Distribution Curves over time

The RCDCs of the proportions of participants exhibiting an hSBA response (≥ LLOQ) for each of the 4 primary MnB test strains and at each sampling time point for all vaccine groups for the evaluable immunogenicity population are provided in Figure 2. In general the RCDCs showed that immune responses increased 1 month after Vaccination 3 and decreased at 6 and 12 months after Vaccination 3 and returned to before Vaccination 1 levels by 24 months after Vaccination 3.

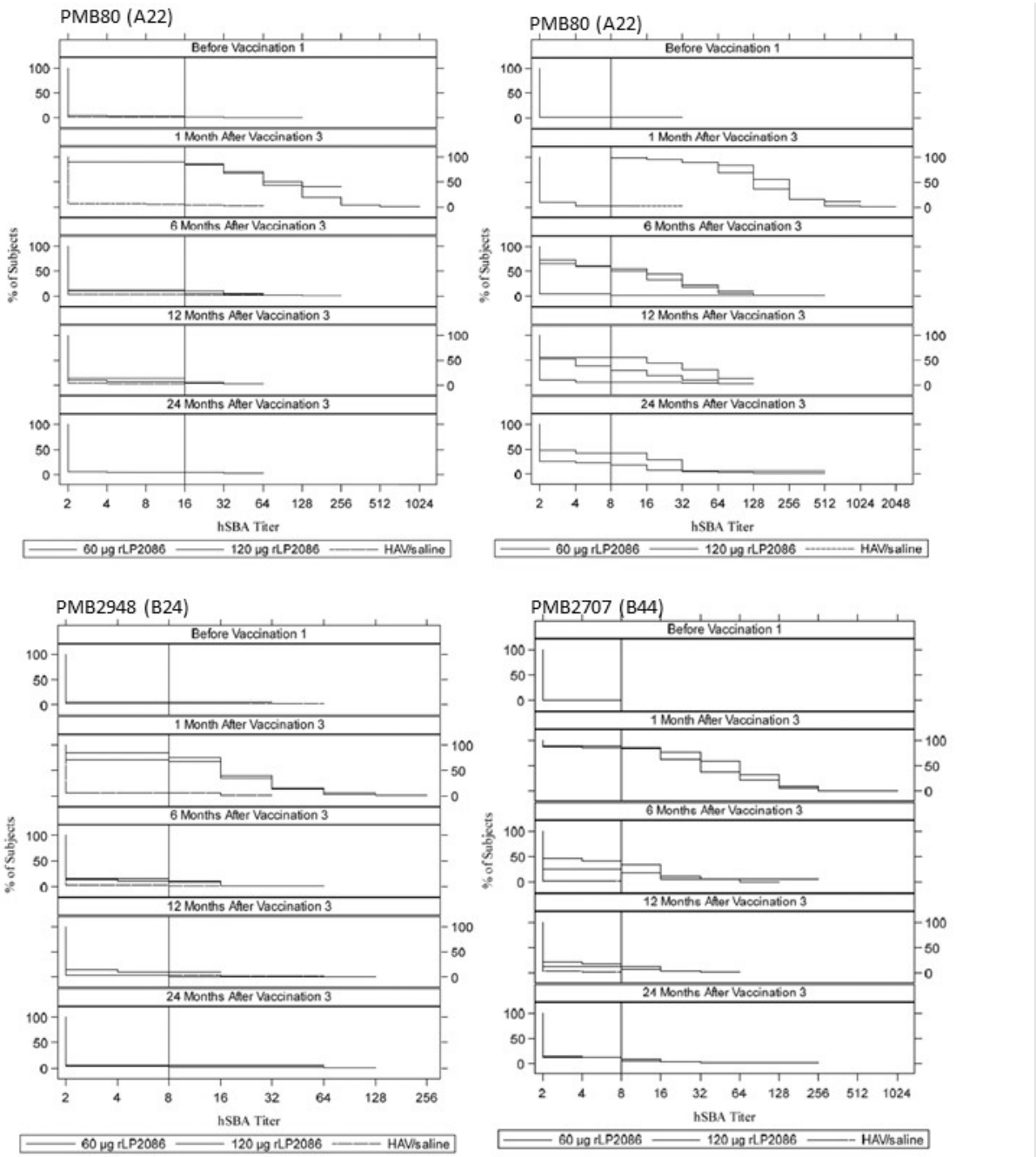


Figure 2 Reverse cumulative distribution curves over time for the 4 primary MenB strains.

Assessor's comments

The RCDCs reflect the poor persistence of hSBA titres. One month after vaccination 3 hSBA titres increased compared to baseline. At 6 months after vaccination 3, hSBA titres are sharply decreased compared to 1 month after vaccination 3 and after 24 months hSBA titres are back to baseline levels.

Booster analysis

The proportion of participants with hSBA titer ≥ LLOQ for primary strains 1 month after booster vaccination were 92.6% for PMB80 (A22), 100% for PMB2001 (A56), 92.8% for PMB2948 (B24), and 95.7% for PMB2707 (B44), see Table 7. The proportion of participants achieving an hSBA titer ≥ LLOQ 1

month after booster vaccination was similar or higher than the proportion of participants achieving an hSBA titer ≥ LLOQ 1 month after Vaccination 3.

Results for the booster mITT population were similar to those of the booster evaluable immunogenicity population.

Table 7 Subjects with hSBA titer ≥ LLOQ for primary strains – Booster evaluable immunogenicity population

Strain (Variant) Sampling Time Point	Vaccine Group (as Randomized) 120 µg rLP2086 N[a]	n[b]	(%)	(95% CI)[c]
PMB80 (A22)				
1 Month after Vaccination 3	69	64	(92.8)	(83.9, 97.6)
Before booster vaccination	69	2	(2.9)	(0.4, 10.1)
1 Month after booster vaccination	68	63	(92.6)	(83.7, 97.6)
PMB2001 (A56)				
1 Month after Vaccination 3	67	67	(100.0)	(94.6, 100.0)
Before booster vaccination	66	10	(15.2)	(7.5, 26.1)
1 Month after booster vaccination	68	68	(100.0)	(94.7, 100.0)
PMB2948 (B24)				
1 Month after Vaccination 3	68	52	(76.5)	(64.6, 85.9)
Before booster vaccination	69	5	(7.2)	(2.4, 16.1)
1 Month after booster vaccination	69	64	(92.8)	(83.9, 97.6)
PMB2707 (B44)				
1 Month after Vaccination 3	67	59	(88.1)	(77.8, 94.7)
Before booster vaccination	67	6	(9.0)	(3.4, 18.5)
1 Month after booster vaccination	69	66	(95.7)	(87.8, 99.1)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation.
Note: LLOQ = 1:16 for A22; 1:8 for A56, B24, and B44.
Note: Serology data for '1 month after Vaccination 3' time point is from the Stage 1 testing campaign.
a. N = number of subjects with valid and determinate hSBA titers for the given strain.
b. n = Number of subjects 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 subjects, using the Clopper and Pearson method.

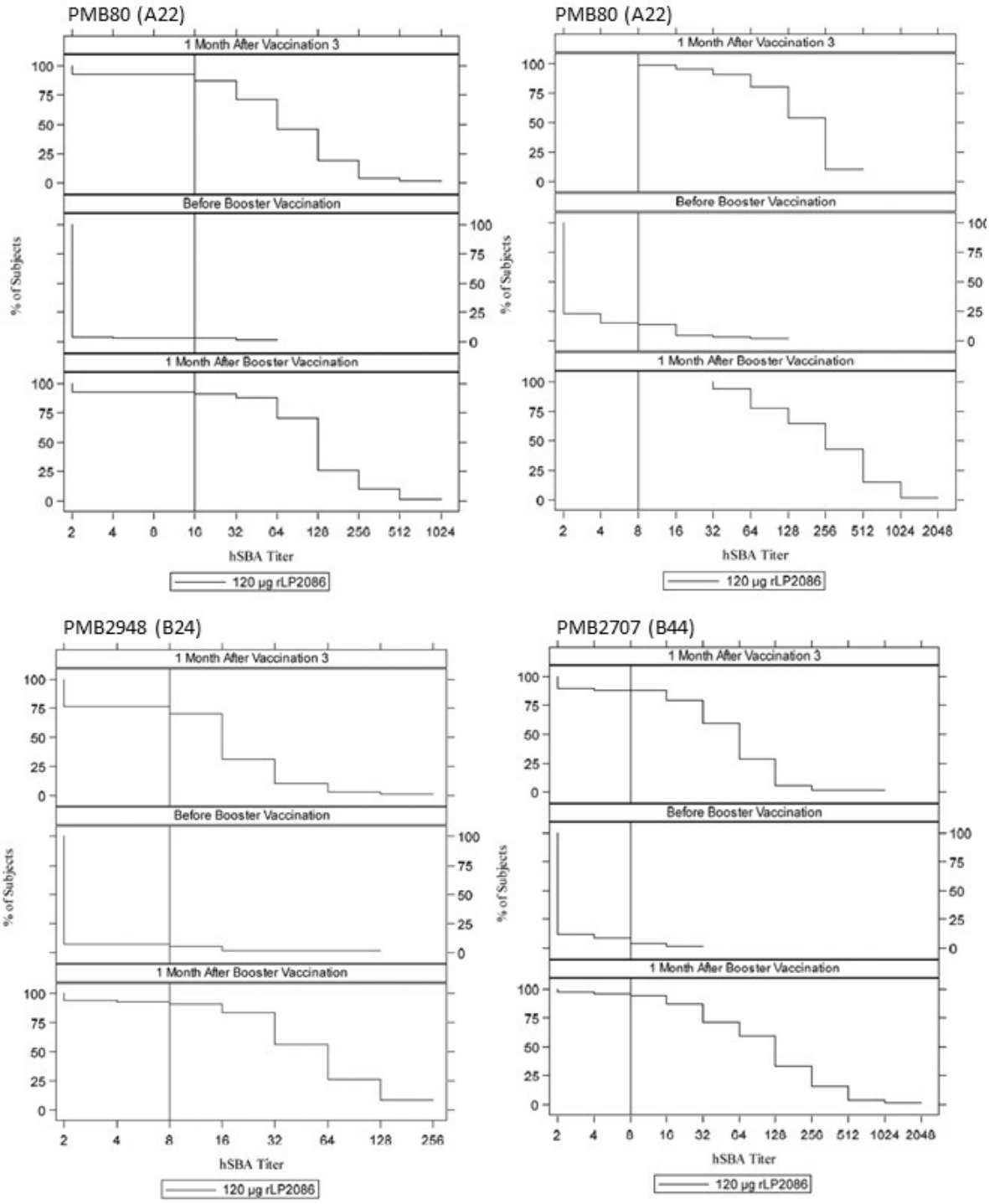
The hSBA GMTs for primary strains 1 month after booster vaccination were 112.1 for PMB80 (A22), 248.3 for PMB2001 (A56), 48.3 for PMB2948 (B24), and 98.6 for PMB2707 (B44), see Table 8.

Table 8 hSBA GMTs for Primary Strains – Booster Evaluable Immunogenicity Population

Strain (Variant) Sampling Time Point	Vaccine Group (as Randomized) 120 µg rLP2086 N[a]	GMT[b]	(95% CI)[c]
PMB80 (A22)			
1 Month after Vaccination 3	69	74.4	(57.6, 96.2)
Before booster vaccination	69	8.4	(7.8, 9.0)
1 Month after booster vaccination	68	112.1	(87.2, 144.2)
PMB2001 (A56)			
1 Month after Vaccination 3	67	157.4	(127.3, 194.7)
Before booster vaccination	66	5.2	(4.4, 6.2)
1 Month after booster vaccination	68	248.3	(192.7, 319.9)
PMB2948 (B24)			
1 Month after Vaccination 3	68	15.2	(12.1, 19.1)
Before booster vaccination	69	4.5	(4.0, 5.1)
1 Month after booster vaccination	69	48.3	(37.6, 62.0)
PMB2707 (B44)			
1 Month after Vaccination 3	67	46.0	(34.4, 61.4)
Before booster vaccination	67	4.4	(4.1, 4.9)
1 Month after booster vaccination	69	98.6	(71.4, 136.2)

Abbreviations: GMT = geometric mean titer; hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation.
Note: LLOQ = 1:16 for A22; 1:8 for A56, B24, and B44. Titers below the LLOQ were set to 0.5 × LLOQ for analysis.
Note: Serology data for '1 month after Vaccination 3' time point is from the Stage 1 testing campaign.
a. N = number of subjects with valid and determinate hSBA titers for the given strain.
b. GMTs were calculated using all subjects with valid and determinate hSBA titers at the given time point.
c. CIs are obtained by exponentiating the limits of CIs for the mean logarithm of the hSBA titers (based on the Student t distribution).

The RCDCs of the proportions of participants exhibiting an hSBA response (≥ LLOQ) for each of the 4 primary MnB test strains and at each sampling time point, for the evaluable immunogenicity population are provided in Figure 3.



Abbreviations: hSBA=serum bactericidal assay using human complement; RCDC=reverse cumulative distribution curve
Note: serology data for '1 month after vaccination 3' time point is from the Stage 1 testing campaign

Figure 3 Booster reverse cumulative distribution curves for the 4 primary MenB strains – Evaluable population

For each group, the percentages for PMB2001 (A56) and PMB2707 (B44) are based on approximately half the participants (those who had the PMB2001 [A56] and PMB2707 [B44] primary strains tested). Likewise, the percentages for PMB80 (A22) and PMB2948 B24) are based on approximately half the participants (those who had the PMB80 [A22] and PMB2948 [B24] primary strains tested). Data were missing for the fewest subjects at 1 month after booster vaccination (≤2 participants for all reasons and groups) and for the most participants at before booster vaccination (≤3 participants for all reasons and groups). The majority of missing results were due to indeterminate reasons.

Assessor's comments

A strong anamnestic response was seen for all 4 primary MenB strains. The proportion of participants with hSBA titres ≥LLOQ was >92.6% for all 4 primary test strains 1 month after the booster dose.

The results of the hSBA GMTs are in line with the proportion of participants achieving hSBA titres ≥LLOQ. The anamnestic response after the booster dose was strong, as hSBA GMTs were higher 1 month after the booster compared to 1 month after the primary series (vaccination 3). This was visualized in the RCDCs for the 4 primary MenB strains.

No clear trends were observed for sex or country.

As stated in the protocol, 2 strains were tested at each blood sampling period for half of the subjects and the other 2 strains in the other half. Missing data was limited 1 month after vaccination and mainly due to the fact that the results of the assay were indeterminate.

6.3. Discussion

The current procedure was performed to update sections 4.8 and 5.1 of the SmPC in order to include immunopersistence and booster data based on final results from study B1971035.

Study B1971035 is a Phase 2, randomized, active-controlled, observer-blinded (sponsor unblinded) multicentre study in children 12 to <24 months of age. This study contains two stages: stage 1, which evaluates primary vaccination with Trumenba and stage 2, which assesses the duration of the immune response to Trumenba and the response to a booster dose of Trumenba. Stage 1 of study B1971035 has been assessed during procedure MEA/H/C/004051/II/0013. The current procedure only assessed data from Stage 2.

Design and conduct of clinical study

Stage 2 is an open-label extension on Stage 1, which is considered acceptable. It is designed to evaluate the duration of the immune response after the primary vaccination series and safety and immunogenicity of a booster dose, both of which are not considered to be impacted by the open-label design of the study as participant already had received multiple doses of Trumenba.

Upon request, the MAH presented information on the 63 participants who were withdrawn after Visit 8 but before booster vaccination in the 120µg group. The immune response appears to be similar when compared between the participants who withdrew and the participants who continued.

The population enrolled in the clinical trial consisted of healthy toddlers, which is considered appropriate. Participants were able to enroll in Stage 2, in case they received 3 doses of 120 µg of bivalent rLP2086 in Stage 1. It is regretted that no information on the anamnestic response after booster dose following a primary vaccination with 60 µg bivalent rLP2086 will be available.

The immunogenicity objectives assessed the immune response by measuring hSBA for 4 MenB strains. As endpoints hSBA GMTs and proportion of participants with hSBA titres ≥ LLOQ, ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥ 1:64, and ≥1:128 at each applicable blood sampling time point will be determined. An hSBA titer of ≥1:4 is the presumptive correlate of protection. The assessment of immunogenicity is considered acceptable.

Persistence data was determined in both subjects aged 12 to <18 months and 18 to <24 months at study entry, which is appreciated. Evaluation of booster dose will be investigated in the age strata combined, which is not fully understood. However, considering the limited number of participants this is not further pursued.

As all analyses are descriptive, no sample size calculation is relevant.

Protocol amendment 3, included removal of the evaluation of immune persistence at 36 and 48 months after vaccination 3 and addition of the evaluation of a booster vaccination, was based on EMA advise. Due to the fact that the protocol was amended while the study was ongoing, participants who received 3 doses of 120 µg of bivalent rLP2086 during Stage 1 could have already completed Visit 11 (24 months after Vaccination 3). In total of the 143 participants, 96.6%, received the booster vaccination 26 months after vaccination 3, while only 3 received the booster vaccination after 25 months and 1 after 24 months. It is considered that the delay of 2 months in booster vaccination for the vast majority is not going to affect the immune response.

Immunogenicity data

Baseline data

In total, 396 participants were received study treatment: 44 participants received 60 µg rLP2086, 220 participants received 120 µg rLP2086 and 132 participants received HAV/saline. The proportion of participants who completed Stage 1 was > 93% and was comparable between the treatment groups. The percentage of participants included in the evaluable immunogenicity population was comparable between groups. The most common reason for exclusion from the evaluable immunogenicity population were participant did not have scheduled prevaccination or postvaccination blood draw and participant received prohibited vaccines.

In total 147 participants in the 120 µg rLP2086 group received a booster vaccination. The most common reason for exclusion from the booster evaluable immunogenicity population was comparable to the persistence evaluable immunogenicity population: participant did not have scheduled prevaccination or postvaccination blood draw.

For the persistence and booster safety population, >51% of participants were female and the vast majority were white and non-hispanic/non-Latino. For the persistence evaluation, the mean age (SD) at first vaccination was 16.6 (4.17) months in the 60 µg rLP2086 vaccine group and 17.6 (3.60) months in the 120 µg rLP2086 vaccine group. The mean age (SD) at booster vaccination was 54.9 (6.23) months.

Outcomes

Persistence of the hSBA response in children aged 12 to 24 months after 3 doses against all of the 4 primary test strains is considered poor, as the proportion of participants with hSBA titres ≥LLOQ reduced substantially from 1 month after primary vaccination to 6 months after primary vaccination. A further reduction was observed from 6 months to 24 months after primary vaccination. One month after three doses against all four primary test strains between 70% and 100% of subjects achieving titres > LLOQ. After six months, the proportion of participants achieving titres ≥LLOQ reduced substantially and ranged from 10.3% (B24) and 59.1% (A56) in the 120 µg rLP2086 group, which reduced further to a range of 3.2% (B24) and 38.7% (A56) at 12 months and 3.7% (A22 and B24) and 22.8% (A56) at 24 months.

The results of the hSBA GMTs are in line with the proportion of participants achieving hSBA titres ≥LLOQ and were visualized in reverse cumulative distribution curves. Where hSBA titres at 6 months after primary vaccination were still slightly higher compared to prevaccination titres, a further reduction was observed from 6 months to 24 months after primary vaccination.

No clear trends in immune persistence were observed between the age groups in the 120 µg rLP2086 group. In general, no differences of >10% in the proportion of participants achieving hSBA titres ≥LLOQ were observed between the 2 age subgroups. In the 60 µg rLP2086 group, more substantial differences were observed, however this is considered to be due to the small number of participants in the 2 age groups.

One month after the booster dose, a strong anamnestic response was seen for all 4 primary MenB strains. The proportion of participants with hSBA titres ≥LLOQ was >92.6% for all 4 primary test strains 1 month after the booster dose.

The results of the hSBA GMTs are in line with the proportion of participants achieving hSBA titres ≥LLOQ, as hSBA GMTs were higher 1 month after the booster compared to 1 month after the primary series (vaccination 3). This was visualized in the RCDCs for the 4 primary MenB strains.

No clear trends were observed for sex or country.

Overall, persistence of hSBA titres in the young children is poor as 6 months after primary vaccination proportion of participants with hSBA titres ≥LLOQ was reduced substantially compared to 1 month after the primary vaccination series and hSBA titres were almost back to baseline values. A booster received approximately 26 months after vaccination 3 of the primary vaccination series was able to induce a strong anamnestic response, with ≥92.6% of participants achieving hSBA titres ≥LLOQ. However, the persistence of this anamnestic response is unknown.

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

Safety endpoints for the booster vaccination analysis included immediate AEs occurring within the first 30 minutes after IP administration, local reactions, systemic events, and use of antipyretic medications within 7 days after booster vaccination, AEs up to 1 month after booster vaccination, and SAEs, MAEs, and NDCMCs to 6 months after booster vaccination.

After the booster vaccination safety data were summarized by combined age strata only. The proportion of participants reporting local reactions, systemic events, and use of antipyretics within 7 days of the booster vaccination were descriptively summarized by group. Two-sided 95% CIs based on the Clopper-Pearson method were presented with the proportions.

Assessor's comments
In general the methods to assess safety are endorsed.

Exposure

The safety population is presented in Table 9. In total 44 subjects received 60 μg of bivalent rLP2086, 220 subjects received 120 μg of bivalent rLP2086 according to the 0,2,6 month schedule, and 132 subjects received HAV vaccine/saline as primary vaccination. Of the 220 subjects that received 3 doses of 120 μg of bivalent rLP2086 during the primary vaccination, 147 received a booster vaccination.

Table 9 Safety population

	Vaccine Group (as Administered)					
	60 µg rLP2086 (N[a]=44)		120 µg rLP2086 (N[a]=220)		HAV/Saline (N[a]=132)	
	n[b]	(%)	n[b]	(%)	n[b]	(%)
Vaccinated in Stage 1[c]	44		220		132	
Stage 1 safety population	44	(100.0)	220	(100.0)	132	(100.0)
Persistence safety population	40	(90.9)	170	(77.3)	N/A	N/A
Received booster vaccination[d]	N/A		147		N/A	
Booster safety population	N/A	N/A	147	(100.0)	N/A	N/A

Abbreviation: N/A = not applicable.
a. N = number of subjects in the specified vaccine group.
b. n = Number of subjects with the specified characteristic.
c. These values were used as the denominator for the percentage calculations for the Stage 1 and persistence safety populations.
d. This value was used as the denominator for the percentage calculation for the booster safety population.

Assessor's comments
For persistence endpoints, the safety population includes all subjects who received at least 1 dose of an investigational product and for whom safety data was available. Of the 174 participants in the 120 µg rLP2086 group that entered stage 2 (see Table 1), 170 completed the visit 11 and contributed safety information.

7.2. Results

Solicited AEs after the booster dose

Local reactions

Local reactions were reported by 77.6% of participants within 7 days after the booster dose. Overall, pain at the injection site was the most commonly reported local reaction. Most local reactions were mild to moderate in severity, see Table 10.

The median onset day for all types of local reactions ranged from 1 to 2 days after booster vaccination. For the booster dose, the median duration of pain at the injection site was 2 days (range of 1 to 11 days); median duration of redness was 2.0 days (range of 1 to 6 days) and median duration of swelling was 1.5 days (range of 1 to 5 days). No participants reported potentiation for any local reactions.

Table 10 Local reactions by maximum severity within 7 days after booster dose – Booster safety population

Local Reaction Severity	Vaccine Group (as Administered) 120 µg rLP2086 N[a]	n[b]	(%)	(95% CI)[c]
Pain at injection site[d]				
Any	147	103	(70.1)	(62.0, 77.3)
Mild	147	45	(30.6)	(23.3, 38.7)
Moderate	147	43	(29.3)	(22.0, 37.3)
Severe	147	15	(10.2)	(5.8, 16.3)
Redness[e]				
Any	147	71	(48.3)	(40.0, 56.7)
Mild	147	33	(22.4)	(16.0, 30.1)
Moderate	147	31	(21.1)	(14.8, 28.6)
Severe	147	7	(4.8)	(1.9, 9.6)
Swelling[e]				
Any	147	49	(33.3)	(25.8, 41.6)
Mild	147	27	(18.4)	(12.5, 25.6)
Moderate	147	22	(15.0)	(9.6, 21.8)
Severe	147	0	(0.0)	(0.0, 2.5)
Any local reaction[f]	147	114	(77.6)	(69.9, 84.0)

a. N = number of subjects with known values in the interval.
b. n = Number of subjects reporting maximum severity of mild, moderate, or severe based on the severity scales.
c. Exact 2-sided CI based upon the observed proportion of subjects, using the Clopper and Pearson method.
d. Mild = Does not interfere with activity, moderate = Interferes with activity, and severe =Prevents daily activity.
e. Mild is 0.5 to 2.0 cm (1 to 4 caliper units), moderate is >2.0 to 7.0 cm (5 to 14 caliper units), and severe is >7.0 cm (>14 caliper units).
f. Any local reaction = any pain at the injection site, any redness, or any swelling.

Systemic reactions

Systemic events were reported by 52.4% participants after booster dose. Most systemic events were mild to moderate in severity. Overall, fatigue (46.3%) was the most commonly reported systemic event after booster vaccination, see Table 11.

Fever of ≥38.0° C, 38.0° C to <38.5° C, and 38.5° C to <39.0° C was reported by 10.2%, 6.1%, and 3.4% of participants respectively after booster vaccination. One participant reported fever of 39.0°C to <39.5°C. No participants reported fever >39.5°C. Use of antipyretic medications were reported by 34.7% of participants in the booster safety population.

The median onset day for all systemic events and use of antipyretic medication ranged from 1 to 2 days after booster vaccination. For the booster dose, the median duration of fever was 1 day (range of 1 to 4 days); median duration of vomiting, diarrhoea and headache was 1 day (range of 1 to 3 days), fatigue was 2 days (range of 1 to 10 days), muscle pain was 1 day (range of 1 to 8 days), joint pain was 1 day (range of 1 to 6 days) and use of antipyretic medication was 1 day (range of 1 to 5 days). No participants reported potentiation for any systemic events.

Table 11 Systemic reactions by maximum severity within 7 days after booster vaccination- booster safety population

Systemic Event Severity	Vaccine Group (as Administered) 120 µg rLP2086 N[a]	n[b]	(%)	(95% CI)[c]
Fever				
≥38.0°C	147	15	(10.2)	(5.8, 16.3)
38.0° to <38.5°C	147	9	(6.1)	(2.8, 11.3)
38.5° to <39.0°C	147	5	(3.4)	(1.1, 7.8)
39.0° to <39.5°C	147	1	(0.7)	(0.0, 3.7)
39.5° to ≤40.0°C	147	0	(0.0)	(0.0, 2.5)
>40.0°C	147	0	(0.0)	(0.0, 2.5)
Vomiting[d]				
Any	147	9	(6.1)	(2.8, 11.3)
Mild	147	7	(4.8)	(1.9, 9.6)
Moderate	147	2	(1.4)	(0.2, 4.8)
Severe	147	0	(0.0)	(0.0, 2.5)
Diarrhea[e]				
Any	147	8	(5.4)	(2.4, 10.4)
Mild	147	7	(4.8)	(1.9, 9.6)
Moderate	147	1	(0.7)	(0.0, 3.7)
Severe	147	0	(0.0)	(0.0, 2.5)
Headache[f]				
Any	147	28	(19.0)	(13.0, 26.3)
Mild	147	11	(7.5)	(3.8, 13.0)
Moderate	147	15	(10.2)	(5.8, 16.3)
Severe	147	2	(1.4)	(0.2, 4.8)
Fatigue[f]				
Any	147	68	(46.3)	(38.0, 54.7)
Mild	147	25	(17.0)	(11.3, 24.1)
Moderate	147	33	(22.4)	(16.0, 30.1)
Severe	147	10	(6.8)	(3.3, 12.2)
Muscle pain (other than muscle pain at the injection site)[f]				
Any	147	24	(16.3)	(10.7, 23.3)
Mild	147	9	(6.1)	(2.8, 11.3)

Systemic Event Severity	Vaccine Group (as Administered) 120 µg rLP2086 N[a]	n[b]	(%)	(95% CI)[c]
Moderate	147	12	(8.2)	(4.3, 13.8)
Severe	147	3	(2.0)	(0.4, 5.8)
Joint pain[f]				
Any	147	15	(10.2)	(5.8, 16.3)
Mild	147	6	(4.1)	(1.5, 8.7)
Moderate	147	9	(6.1)	(2.8, 11.3)
Severe	147	0	(0.0)	(0.0, 2.5)
Use of antipyretic medication	147	51	(34.7)	(27.0, 43.0)
Any systemic event[g]	147	77	(52.4)	(44.0, 60.7)

Abbreviation: IV = intravenous.
a. N = number of subjects with known values after the vaccination.
b. n = Number of subjects reporting maximum severity of mild, moderate, or severe based on the severity scales after the vaccination.
c. Exact 2-sided confidence interval (Clopper and Pearson) based upon the observed proportion of subjects.
d. Mild = 1 to 2 times in 24 hours, moderate = >2 times in 24 hours, and severe = requires IV hydration.
e. Mild = 2 to 3 loose stools in 24 hours, moderate = 4 to 5 loose stools in 24 hours, and severe = 6 or more loose stools in 24 hours.
f. Mild = does not interfere with activity, moderate = some interference with activity, and severe = prevents daily routine activity.
g. "Any systemic event" does not include consideration of the use of antipyretic medication.

Assessor's comments

The majority of participants reported local and systemic reactions. Most reactions were mild to moderate in intensity and of short duration (<3 days). No potentiation was observed after the booster dose.

The most commonly reported local reaction after the booster dose was pain at the injection site (70.1%), followed by redness (48.3%) and swelling (33.3%).

The most commonly reported systemic reaction after the booster dose was fatigue (46.3%), followed by headache (19.0%) and muscle pain (16.3%). Any fever was experienced by 10.2% of participants. One participant (0.7%) experienced fever of 39.0°C to <39.5°C, while none of the participants reported fever >39.5°C. The fever was usually of short duration, median 1 day (range 1 to 4 days), and use of antipyretic medications was reported by 51 participants (34.7%) in the booster safety population during 1 day.

No clear trends were observed for sex or country.

Adverse events

Persistence safety analysis

There were a total of 7 AEs reported after Visit 8 and prior to booster vaccination by 7 participants (3 severe, 1 moderate, and 3 mild), none were assessed as related to IP by the investigator. No participants reported AEs leading to study discontinuation after Visit 8 [6 months after Vaccination 3] and prior to booster vaccination.

One participant who received 120 µg rLP2086 reported 1 AE of scarlet fever within 48 hours after blood draw at Visit 11 (24 months after Vaccination 3).

Assessor's comments

In total 7 participants experienced AEs between visit 8 and the booster vaccination. Three participants experienced AEs in the SOC infections and infestations (all severe), 2 in the SOC Respiratory, thoracic and mediastinal disorders (1 severe and 1 mild), 1 in Skin and subcutaneous tissue disorders (moderate) and Metabolism and nutrition disorders (mild). As all occurred over 6 months after the primary vaccination series, none were considered related to the IP, which can be agreed. None led to study discontinuation.

One participant experienced an NDCMC of fructose malabsorption. A prescription of a low fructose diet resulted in the abatement of the subject's symptoms. The NDCMC was not considered related to the vaccine.

Booster safety analysis

From booster vaccination up through 1 month after booster vaccination 20 (13.6%) participants reported at least 1 AE, of which 3 participants (2.0%) reported 6 events related to IP as assessed by the investigator.

A total of 20 (13.6%) participants reported 26 AEs. AEs were most commonly reported in the SOC of infections and infestations in 18 participants (12.2%). The most frequently reported AEs by PT were viral upper respiratory tract infection and upper respiratory tract infection (3.4% and 2.0%, respectively). All other AE PTs were reported in ≤2 participants.

AEs reported from booster vaccination up through 1 month after booster vaccination and assessed by the investigator as related to the IP are presented in Table 12. A total of 3 participants (2.0%) reported 6 AEs related to IP as determined by investigator, all related AEs were mild in severity as assessed by the investigator. The most frequently reported AEs by PT were irritability and decreased appetite (2 participants [1.4%], each). All other AE PTs were reported in 1 participants each.

Table 12 Related Adverse Events Reported During the Booster Vaccination Phase – Booster Safety Population

System Organ Class[b] Preferred Term	Vaccine Group (as Administered) 120 µg rLP2086 (N[a]=147) n[c]	(%)	Number of Events[d]
Any event	3	(2.0)	6
Metabolism and nutrition disorders	2	(1.4)	2
Decreased appetite	2	(1.4)	2
Psychiatric disorders	3	(2.0)	3
Irritability	2	(1.4)	2
Restlessness	1	(0.7)	1
Respiratory, thoracic and mediastinal disorders	1	(0.7)	1
Rhinorrhoea	1	(0.7)	1

Note: The classification of adverse events is based on MedDRA (Version 23.0). Adverse events reported before the booster vaccination were excluded, unless the severity worsened after vaccination.
Note: The booster vaccination phase is from the booster vaccination (Visit 12) through 1 month after the booster vaccination (Visit 13).
a. N = number of subjects in the specified group. This value was used as the denominator for the percentage calculations for the vaccine group.
b. Subjects are only counted once within a system organ class even though a subject may report multiple adverse events under different preferred terms.
c. n = Number of subjects reporting at least 1 occurrence of the event specified. "Any event" represents the number of subjects reporting at least 1 occurrence of any kind of event.
d. The total number of occurrences of the event specified. Subjects can be represented more than once. "Any event" and "system organ class" event counts are the sum of individual occurrences within that category.

Assessor's comments

In total 20 participants reported at least 1 AE (26 in total). Most AEs were mild to moderate in severity. The most commonly reported AEs were in the SOC of infections and infestations, which was to be expected in this population.

Of the 26 AEs reported, 6 AEs experienced by 3 participants were considered to be related to the IP. All of these were considered mild in severity. The most commonly reported related AEs occurred in the SOC psychiatric disorders (irritability n=2 and restlessness n=1), followed by metabolism and nutrition disorders (decreased appetite n=2) and respiratory, thoracic and mediastinal disorders (rhinorrhoea n=1).

None of the AEs led to study discontinuation.

Serious adverse events/deaths/other significant events

Deaths

No participants died during the period covered in this report (after Visit 8 [6 months after Vaccination 3] to 6 months after booster vaccination).

SAEs

SAEs reported from booster vaccination up through 6 months after booster vaccination are presented in Table 13. Two (1.4%) participants reported a total of 2 SAEs from booster vaccination up through 6 months after booster vaccination (1 SAE of constipation and 1 SAE of rhinovirus infection). No SAEs reported from booster vaccination up through 6 months after booster vaccination were related to IP as assessed by investigator.

Table 13 Subjects Reporting at Least 1 Serious Adverse Event During Booster Phase for Each Analysis Interval – Booster Safety Population

Interval End Point	Vaccine Group (as Administered) 120 µg rLP2086 N[a]	n[b]	(%)	(95% CI)[c]	No. of Events
During the booster vaccination phase[d]					
Any	147	1	(0.7)	(0.0, 3.7)	1
Related[g]	147	0	(0.0)	(0.0, 2.5)	0
During the booster follow-up phase[e]					
Any	147	1	(0.7)	(0.0, 3.7)	1
Related[g]	147	0	(0.0)	(0.0, 2.5)	0
Throughout the booster phase[f]					
Any	147	2	(1.4)	(0.2, 4.8)	2
Related[g]	147	0	(0.0)	(0.0, 2.5)	0

a. N = number of subjects who are in the safety population for the specified analysis interval. The values in this column are used as the denominators for the percentage calculations.
b. n = Number of subjects with at least 1 event for the specified analysis interval.
c. Exact 2-sided CI based upon the observed proportion of subjects, using the Clopper and Pearson method.
d. The booster vaccination phase is from the booster vaccination (Visit 12) through 1 month after the booster vaccination (Visit 13).
e. The booster follow-up phase is from 1 month after the booster vaccination (Visit 13) through 6 months after the booster vaccination (Visit 14).
f. The booster phase is from the booster vaccination (Visit 12) through 6 months after the booster vaccination (Visit 14).
g. Relatedness of AE is related to investigational product as assessed by the investigator.

MAEs

In total 11 participants experienced 12 MAEs, see Table 14. MAE were most commonly reported in the SOC of infections and infestations (10 [6.8%] participants) and the most common MAE by PT was upper respiratory tract infection and pharyngitis (2 participants each). All other MAEs were reported by 1 participant each. None of the MAEs reported within 6 months after booster vaccination were related to the IP as assessed by the investigator.

Table 14 Medically Attended Adverse Events Reported During the Booster Phase – Booster Safety Population

System Organ Class[b] Preferred Term	Vaccine Group (as Administered) 120 µg rLP2086 (N[a]=147) n[c]	(%)	Number of Events[d]
Any event	11	(7.5)	12
Infections and infestations	10	(6.8)	10
Croup infectious	1	(0.7)	1
Erythema infectiosum	1	(0.7)	1
Influenza	1	(0.7)	1
Pharyngitis	2	(1.4)	2
Tonsillitis	1	(0.7)	1
Upper respiratory tract infection	2	(1.4)	2
Viral infection	1	(0.7)	1
Viral pharyngitis	1	(0.7)	1
Injury, poisoning and procedural complications	1	(0.7)	1
Head injury	1	(0.7)	1
Skin and subcutaneous tissue disorders	1	(0.7)	1
Dermatitis atopic	1	(0.7)	1

Note: The classification of adverse events is based on MedDRA (Version 23.0). Adverse events reported before the booster vaccination were excluded, unless the severity worsened after vaccination.
Note: The booster phase is from the booster vaccination (Visit 12) through 6 months after the booster vaccination (Visit 14).
a. N = number of subjects in the specified group. This value was used as the denominator for the percentage calculations for the vaccine group.
b. Subjects are only counted once within a system organ class even though a subject may report multiple adverse events under different preferred terms.
c. n = Number of subjects reporting at least 1 occurrence of the event specified. "Any event" represents the number of subjects reporting at least 1 occurrence of any kind of event.
d. The total number of occurrences of the event specified. Subjects can be represented more than once. "Any event" and "system organ class" event counts are the sum of individual occurrences within that category.

Assessor's comments
No deaths occurred during the study.

The proportion of participants with SAEs from booster vaccination up through 6 months after booster vaccination was low, 1.4%. In total 2 SAEs occurred: 1 SAE of constipation at Day 82 after booster vaccination and 1 SAE of rhinovirus infection occurring 178 days after booster vaccination. Upon request the MAH provided narratives for the SAEs. The SAEs are considered unrelated to the study drug.

MAEs occurred in 7.5% of participants. In total 12 MAEs occurred, of which none were considered related to the booster vaccine according to the investigator. The MAH provided narratives for the incidence of acute pharyngitis occurring 2 days after booster vaccination, atopic dermatitis occurring 11 days after booster vaccination, and head injury occurring 11 days after booster vaccination to enable thorough assessment of the relatedness. It is agreed that none of the MAEs was considered related to the study drug.

Discontinuation

No participants were withdrawn during the period covered in this report (after Visit 8 [6 months after Vaccination 3]) for safety-related reasons.

Assessor's comments
The fact that none of the participants discontinued due to AE is considered reassuring.

7.3. Discussion

In total 44, 170 and 132 participants were enrolled in the persistence safety population in the 60 µg rLP2086, 120 µg rLP2086 and HAV/saline group respectively. For persistence endpoints, the safety population includes all subjects who received at least 1 dose of an investigational product and for whom safety data was available. Of the 174 participants in the 120 µg rLP2086 group that entered stage 2 (see Table 1), 170 completed the visit 11 and provided safety information.

Of the 170 participants in the 120 µg rLP2086 group of the persistence safety population, 147 received a booster vaccination.

Local and systemic reactions

After the booster vaccine, the majority of participants reported local and systemic reactions. Most reactions were mild to moderate in intensity and of short duration (<3 days). No potentiation was observed after the booster dose. Local reactions were reported by 77.6% of participants, with pain at the injection site (70.1%) being the most commonly reported, followed by redness (48.3%) and swelling (33.3%). This is in line with the results obtained during study B1971017, during which healthy subjects aged ⩾24 months to <10 years were treated with 120 µg rLP2086, although frequency of the local reactions were lower after the booster dose compared to the primary vaccination series. In total 77 participants (52.4%) experienced a systemic reaction. Most of the systemic reactions were mild to moderate in severity and of short duration (≤2 days). The most commonly reported systemic reaction after the booster dose was fatigue (46.3%), followed by headache (19.0%) and muscle pain (16.3%). Again this is in line with the results obtained during study B1971017, although frequency of the local reactions were lower after the booster dose compared to the primary vaccination series.

Any fever was experienced by 10.2% of participants. One participant (0.7%) experienced fever of 39.0°C to <39.5°C, while none of the participants reported fever >39.5°C. The fever was usually of short duration, median 1 day (range 1 to 4 days), and use of antipyretic medications was reported by 51

participants (34.7%) in the booster safety population during 1 day. Again, the frequency of fever was lower compared to the results for study B1971017, where 24.5% of participants reported fever. During study B1971017 it was already observed that fever rates declined with subsequent vaccinations.

Trumenba is was found to be a reactogenic vaccine with a high proportion of subjects reporting local and systemic reactions.

Other AEs

During the persistence analysis period between visit 8 and the booster vaccination, 7 participants experienced AEs, of which none were considered related to the IP, which can be agreed. None led to study discontinuation.

After the booster vaccination, 20 participants reported at least 1 AE (26 in total). Severe events were rare, as were related events. The most commonly reported AEs were in the SOC of infections and infestations, which was to be expected in this population. In total, 6 AEs experienced by 3 participants were considered to be related to the booster with Trumenba, which were all considered mild in severity. The most commonly reported related AEs occurred in the SOC psychiatric disorders (irritability n=2 and restlessness n=1), followed by metabolism and nutrition disorders (decreased appetite n=2) and respiratory, thoracic and mediastinal disorders (rhinorrhoea n=1). None of the AEs led to study discontinuation.

No deaths occurred during the study. The proportion of participants with SAEs from booster vaccination up through 6 months after booster vaccination was low, 1.4%. In total 2 SAEs occurred: 1 SAE of constipation at Day 82 after booster vaccination and 1 SAE of rhinovirus infection occurring 178 days after booster vaccination. MAEs occurred in 7.5% of participants. In total 12 MAEs occurred, of which none were considered related to the booster vaccine according to the investigator.

Upon request, the MAH presented information on the 63 participants who were withdrawn after Visit 8 but before booster vaccination in the 120µg group. A slight trend was observed that participants who withdrew experienced slightly more mild to moderate AEs during the vaccination period compared to participants who continued. This slight increase in mild to moderate AEs in the participants who withdrew is considered not to impact the benefit/risk profile of the product for use as a booster vaccine. In addition, the safety profile of the product is not expected to alter, therefore, there is no need to include information on this subset of participants in the SmPC.

In conclusion, Trumenba is considered a reactogenic vaccine, with the majority of participants reporting local and systemic reactions. Most reactions were mild to moderate in intensity and of short duration (<3 days). The safety profile of the persistence analysis and booster vaccination are generally in line with the primary vaccination during Stage 1, although the frequency of reactions decreased with subsequent vaccinations. No new safety signals were observed either during the persistence analysis period or after the booster dose.

8. PRAC advice

Not applicable.

9. Changes to the Product Information

As a result of this variation, sections 4.8 and 5.1 of the SmPC are being updated to include immunopersistence and booster data based on final results from study B1971035.

In addition, the MAH is also taking this opportunity to introduce editorial changes in the SmPC and to

update the list of local representatives in the Package Leaflet.

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

10. Request for supplementary information

10.1. Major objections

Not applicable.

10.2. Other concerns

Clinical aspects

1) The MAH is asked to present justification for the exclusion of Finland from the booster dose evaluation.
2) Stage 2 was open-label. Therefore, the MAH is asked to analyse whether participants who were no longer willing to participate had more/more severe AEs/RRIs during Stage 1 of the study and/or different immune response compared to the participants who are still willing to participate and discuss the impact of the observed difference on safety and immunogenicity outcomes, supported by adequate sensitivity analyses for example using multiple imputation.
3) Participants in Finland are not included in the persistence safety population. The MAH is asked to present persistence immunogenicity and safety data with the participants enrolled in Finland included, unless the MAH has a very strong reason not to include these participants.
4) The MAH is asked to discuss the apparent discrepancy between the 174 participants in the 120 µg rLP2086 group that entered stage 2 (see Table 1) and the 170 that were included in the persistence safety population (see Table 9).
5) In total 2 SAEs occurred: 1 SAE of constipation at Day 82 after booster vaccination and 1 SAE of rhinovirus infection occurring 178 days after booster vaccination. The MAH is asked to provide narratives for the SAEs.
6) The MAH is requested to provide narratives for the incidence of cute pharyngitis occurring 2 days after booster vaccination, atopic dermatitis occurring 11 days after booster vaccination, head injury occurring 11 days after booster vaccination and croup occurring 5 days after booster vaccination to enable thorough assessment of the relatedness.

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

11.1. Major objections

Not applicable.

11.2. Other concerns

Clinical aspects

Question 1

The MAH is asked to present justification for the exclusion of Finland from the booster dose evaluation.

Summary of the MAH's response

During 2018, and in agreement with the European Medicines Agency (EMA), Study B1971035 was amended (Protocol Amendment 3) to reduce the immunopersistence phase from 4 years to 2 years and add a booster dose at 2 years following the completion of the primary vaccination series.

During implementation of this amendment, the Sponsor concluded that there were adequate numbers of potential participants to meet the target sample size for the booster vaccination at sites in Australia, Poland, and Czech Republic and because a very small number of participants (14) remained on study in Finland at that time, Finland would not participate in the booster extension phase of the study. Consequently, no subjects in Finland progressed beyond the 12 months post primary series blood draw visit (last Stage 1 visit) and no Finnish subjects progressed to Stage 2 of the study.

Assessment of the MAH's response

The explanation by the MAH is acknowledged. As adequate numbers of potential participants to meet the target sample size for the booster vaccination remained in the other countries and in Finland only 14 participants remained in the study, the MAH decided to exclude Finland from the substantial amendment. Considering that the study was descriptive, and the sample size not driven by hypothesis testing, it can be understood that the participants in Finland were excluded from this change in study design.

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

Stage 2 was open-label. Therefore, the MAH is asked to analyse whether participants who were no longer willing to participate had more/more severe AEs/RRIs during Stage 1 of the study and/or different immune response compared to the participants who are still willing to participate and discuss the impact of the observed difference on safety and immunogenicity outcomes, supported by adequate sensitivity analyses for example using multiple imputation.

Summary of the MAH's response

Out of 220 participants randomized to receive bivalent rLP2086 120 µg, very few withdrew or were not willing to continue participation by choice throughout the duration of Stage 1 of the study and continue onto Stage 2. As a result, Pfizer respectfully proposes that separate summaries of the safety in Stage 1 for those who withdrew in Stage 1 due to unwillingness to participate in Stage 2 compared with rest of population are not considered informative. The numbers of subjects randomized to receive bivalent rLP2086 120 µg as they progressed or withdrew through the primary series stage through entry into Stage 2 are

described below:

Of the 220 subjects randomized to receive bivalent rLP2086 120 µg:

- 212 completed all 3 primary vaccinations (96.4%; compared to 97.7% in HAV/Saline group). One subject discontinued due to unwillingness to participate further because the family moved to an area distant from the study site during this period.
- 210 continued through 6 months after primary series completion (95.5%; compared to 96.2% in HAV/Saline group). Two subjects discontinued due to withdrawal of consent during this period.

Between the 6 months after completion of the primary series timepoint and Stage 2 entry timepoint (24 month post primary series), 16 subjects withdrew from the study for the reasons listed below:

- 14 subjects from Finland did not progress to Stage 2 by design as indicated in Response 1 (Section 2.1).
- 2 subjects were unwilling to progress to Stage 2 due to their caregiver withdrawing consent.

Given the very low overall withdrawal rate during the primary vaccination series phase of the study and the fact that only 5 subjects did not progress by choice / were unwilling to progress during Stage 1 into Stage 2, Pfizer respectfully proposes that separate summaries of the safety in Stage 1 for those who withdrew due to "unwillingness to participate in Stage 2" compared with rest of population will not be informative. Instead, Pfizer provides a listing below in Table 1 with detailed disposition information for the 5 subjects that were "unwilling to progress to Stage 2".

Group (as Administered)	Subject	Last Vax No.	Rel Day	Last Visit Completed	Discontinuation Phase	Explanation
120 µg rLP2086	Subject 1	3	29	Visit 7	WITHDRAWN DURING POST-THERAPY FOLLOW-UP PERIOD	NO LONGER WILLING PARTICIPATE IN STUDY
	Subject 2	3	457	Visit 8	WITHDRAWN DURING POST-THERAPY FOLLOW-UP PERIOD	WITHDREW CONSENT
	Subject 3	3	385	Visit 8	WITHDRAWN DURING POST-THERAPY FOLLOW-UP PERIOD	WITHDREW CONSENT
	Subject 4	1	71	Visit 4	WITHDRAWN DURING ACTIVE TREATMENT PERIOD	WITHDREW CONSENT
	Subject 5	1	49	Visit 4	WITHDRAWN DURING ACTIVE TREATMENT PERIOD	WITHDREW CONSENT

Abbreviations: Rel Day = relative day; Vax = vaccination.

Assessment of the MAH's response

The MAH states that only 5 subjects did not progress by choice / were unwilling to progress during Stage 1 into Stage 2. It is agreed that for 5 subjects there is no need to make separate tables.

In principle the question was on the fact that from 220 participants who were randomized, 212 completed all 3 primary vaccinations and 210 continued through 6 months follow-up. However, only 148 participants entered the booster stage and 147 participants received the booster vaccination. It is acknowledged that the question was not posed clearly, therefore, the MAH is asked to present information on the following:

In total, 63 participants were withdrawn after Visit 8 but before booster vaccination from the 120µg group according to the disposition of subjects (Table 1). For these participants who did not continue with the booster vaccination (28.6% of participants in the study), the MAH is asked to determine whether they had more/more severe AEs/RRIs during Stage 1 of the study and/or different immune response compared to the participants who did continue and discuss the impact of the observed difference on safety and immunogenicity outcomes, supported by adequate sensitivity analyses for example using multiple imputation.

Conclusion: issue *not* solved.

☐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

Participants in Finland are not included in the persistence safety population. The MAH is asked to present persistence immunogenicity and safety data with the participants enrolled in Finland included, unless the MAH has a very strong reason not to include these participants.

Summary of the MAH's response

Participants from Finland only took part in Stage 1 of the study as described in responses 1 and 2. The evaluable immunogenicity population was used to report out immunopersistence and Finnish participants were eligible to be included in this population for the duration of their participation in the study, which is through 12 months post primary series completion time point.

For the persistence safety analyses, Finnish participants were not included in the analyses since these subjects did not contribute safety data at the Visit 11 (24 months post primary series time point), which was a requirement for entry into the persistence safety population. Pfizer provides a revised listing (See Table 2) which now includes AEs reported during the persistence stage for all subjects reporting any safety data during this stage, regardless of whether they contributed safety data at the 24 months post primary series time point. The revised listing added data for only 2 additional subjects reporting safety data during this stage of which only one participant was from Finland. The persistence safety interval data provided in Table 2 for the bivalent rLP2086 120 µg group is identical to data provided for this group in the CSR listing for this interval and the new data added is one AE for bivalent rLP2086 60 µg and one for HAV/saline group.

Table 2. Listing of Adverse Events Reported After Visit 8 and Prior to booster Vaccination – Includes any Subject who Reported Safety Data During this Stage

Vaccine Group (as Administered)	Subject	SOC	Preferred Term/AE Investigator Text	Vax No.	Onset Date (Rel Day)	Dur (Days)[a]	Severity[b]	Vax Rel[c]	Cause of AE[d]	Action[e]: Study Vaccine Dose/Subject	AE Still Present	IMM/SAE/MAE/ NDCMC Flag
60 µg rLP2086	Subject 6	RESP	Rhinitis allergic/ ALLERGIC RHINITIS	3/FU	Day 210	30	MILD	No	O	N/T	Resolved (Day 240)	No/No/No/No
120 µg rLP2086	Subject 7	INFEC	Cellulitis/ CELLULITIS - LEFT KNEE	3/FU	Day 272	9	SEV	No	OI	N/T	Resolved (Day 281)	No/Yes/No/No
	Subject 8	INFEC	Influenza/ INFLUENZA A INFECTION	3/FU	Day 279	15	SEV	No	OI	N/T	Resolved (Day 294)	No/Yes/No/No
	Subject 9	GASTR	Malabsorption/ FRUCTOSE MALABSORPTION	3/FU	Day 534	C	MILD	No	O	N/O	Yes	No/No/Yes/Yes
	Subject 10	SKIN	Urticaria/ URTICARIA	3/FU	Day 892	14	MOD	No	O	N/T	Resolved (Day 906)	No/No/No/No
	Subject 11	INFEC	Scarlet fever/ SCARLATINA	3/FU	Day 702	11	MILD	No	OI	N/T	Resolved (Day 713)	No/No/Yes/No
	Subject 12	RESP	Sleep apnoea syndrome/ SLEEP APNOEA	3/FU	Day 297	C	SEV	No	O	N/T	Yes	No/Yes/No/No
	Subject 13	RESP	Cough/ COUGH	3/FU	2019	C	MILD	No	O	N/T	Yes	No/No/Yes/No
HAV/saline	Subject 14	INFEC	Otitis media/ OTITIS MEDIA	3/FU	Day 184	10	MILD	No	O	N/T	Resolved (Day 194)	No/No/Yes/No

Abbreviations: Dur = duration; Imm = immediate adverse event; FU = follow-up; MAE = medically attended adverse event; NDCMC = newly diagnosed chronic medical condition; Rel Day = relative day; Vax = vaccination; Vax Rel = vaccine related. Refer to the AE legend page (Listing 16.2.7.1) for additional definitions. Note: The classification of adverse events is based on the Medical Dictionary for Regulatory Activities (MedDRA; Version 20.0).

a. C = continuing; U = unknown.
b. MOD = moderate; SEV = severe.
c. Vax Rel: Relationship to study vaccine as assessed by the investigator.
d. Cause of AE: C = concomitant treatment; I = injection/procedure related; OI = other illness; O = other.
e. Action: Study Vaccine Dose/Subject: N = no action taken; O = other; P = permanently discontinued; T = treatment given; W = withdrawn from the study.

Assessment of the MAH's response

The confirmation that participants from Finland were eligible to be included in the immunopersistence population for the duration of their participation up to 12 months post vaccination is appreciated. It is still not fully understood why participation for the Finish participants did not continue after 1 years as the protocol prior to amendment 3 indicated an immunopersistence period of 4 years and Finland was excluded

from amendment 3. However, considering that only 14 participants remained in Finland the issue is not further pursued.

The additional safety data is appreciated. Two additional mild AEs, which were considered not related to the study vaccine, were included. As described above, it is not fully understood why the Finish participants did not contribute safety data at Visit 11 or even after that. However, considering the small number of participants, the issue is not further pursued.

Conclusion: Issue not further pursued.

☐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 MAH is asked to discuss the apparent discrepancy between the 174 participants in the 120 µg rLP2086 group that entered stage 2 (see Table 1) and the 170 that were included in the persistence safety population (see Table 9).

Summary of the MAH's response

The persistence safety population is defined to include participants who received at least 1 dose of investigational product and for whom safety information is available at visit 11 (24 months post primary series time point). Of the 174 participants who entered stage 2, 4 did not contribute any safety data at visit 11 and were therefore not included in the persistence safety population. in response 3 for all safety data recorded during the persistence stage.

Assessment of the MAH's response

The response of the MAH is appreciated.

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 5

In total 2 SAEs occurred: 1 SAE of constipation at Day 82 after booster vaccination and 1 SAE of rhinovirus infection occurring 178 days after booster vaccination. The MAH is asked to provide narratives for the SAEs.

Summary of the MAH's response

One participant with a prior medical history of eczema, bronchiolitis, tonsillitis, tonsillar hypertrophy, otitis media, mite allergy, allergic rhinitis, and sleep terror received 120 µg bivalent rLP2086 on Day 1, Day 43, Day 123, and Day 938 after study enrolment. During the primary vaccination and follow-up phase, the participant experienced several self-limiting unrelated adverse events including acute bronchitis (11 days after Vaccination 1), 2 episodes of rhinorrhea (44 days after Vaccination 1 and 28 days after Vaccination 3 respectively), otitis media (3 days after Vaccination 2), viral upper respiratory infections (35 days after Vaccination 2), 2 episodic wheezing (10 days and 60 days after Vaccination 2 respectively), and croup (170 days after Vaccination 3). The participant experienced another viral upper respiratory infection 11 days following the booster dose. Seventy-eight days following the booster vaccination, the participant underwent

a scheduled tonsillectomy and adenoidectomy and was discharged on oxycodone as needed for pain every 4 hours. Three days later, the participant developed abdominal pain and constipation and was subsequently admitted to the hospital 2 days after these symptoms developed for constipation, vomiting and mild dehydration and was treated with IV hydration antiemetics and laxatives. The participant was discharged home the next day on polyethylene glycol and their constipation was considered resolved within a week. The constipation was considered a side effect of the oxycodone by the investigator.

Another participant with a prior medical history of eczema received 120 µg bivalent rLP2086 on Day 1, Day 49, Day 153, and Day 960 after study enrolment. During the primary vaccination and follow-up phase the participant experienced one episode of rhinorrhea (9 days after Vaccination 1), two episodes of otitis media (21 days after Vaccination 1 and 34 days after Vaccination 2) and two episodes of upper respiratory infections (84 days and 149 days respectively after Vaccination 3), all of which were managed on an outpatient basis. 178 days following the booster dose, the participant developed a rash and upper respiratory symptoms and was admitted to hospital 3 days laterIV hydration and empiric antibiotics (ceftriaxone). Oral pain was managed with lidocaine, fever with paracetamol, and urticaria with cetirizine. The clinical course of the participant was unremarkable, and the participant was discharged home 2 days later at which time the participant was considered recovered. The investigator reported the event was not related to the investigational vaccine.

Assessment of the MAH's response

The presentation of the narratives for the SAEs is appreciated. The SAEs are considered unrelated to the vaccination.

It is agreed with the investigator that the SAE of constipation at Day 82 after booster vaccination is unrelated to the study drug. A likely cause of the SAE is use of oxycodone. Oxycodone was used when SAE occurred and constipation, vomiting, dehydration and abdominal pain are known (very) common AEs.

The SAE of rhinovirus infection occurring 178 days after booster vaccination is also unlikely related to the study drug.

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 6

The MAH is requested to provide narratives for the incidence of acute pharyngitis occurring 2 days after booster vaccination, atopic dermatitis occurring 11 days after booster vaccination, head injury occurring 11 days after booster vaccination and croup occurring 5 days after booster vaccination to enable thorough assessment of the relatedness.

Summary of the MAH's response

Acute Pharyngitis:

One participant with no past medical history received the booster vaccination of 120 µg bivalent rLP2086 on Day 1022 after study enrolment. The participant returned to the clinic the following day with fever and was diagnosed with a mild case of acute pharyngitis by the investigator and empirically treated with a 7-day course of amoxicillin. Symptoms resolved within 4 days. During the 7 days post booster vaccination, the participant experienced fever on Day 1 (38.7°C) and Day 2 (38.2°C), moderate injection site pain, swelling (11 caliper units) and redness (11 caliper units) on Day 2 at the injection site, moderate fatigue

on Day 2, severe muscle pain on Day 2 and no headache, vomiting, diarrhea, or joint pain; mild swelling (3 caliper units) and mild fatigue on Day 3. No additional information was provided. The pharyngitis was considered to be of likely viral etiology and unrelated to the investigational vaccine by the investigator.

Atopic Dermatitis:

One participant with a history of recurrent otitis media, lactose intolerance, and rhinitis received the booster vaccination of 120 µg bivalent rLP2086 on Day 1358 after study enrolment. During the 7 days post booster vaccination interval, the participant experienced mild injection site pain intermittently and mild swelling (1 caliper unit) on Day 1, mild fatigue on Days 3 and 4, and no other reactogenicity events. The participant's parents reported unspecified symptoms starting on Day 2 following booster vaccination for which medical attention was not sought but for which the investigator attributed the symptoms to a viral upper respiratory infection. On Day 10, the participant still had symptoms of the upper respiratory infection and presented with a skin rash which the primary care physician diagnosed as atopic dermatitis related to concurrent viral infection. The participant was treated with paracetamol and loratadine and the atopic dermatitis was considered resolved within approximately 1 month of onset. As the onset of the atopic dermatitis occurred after resolution of a relatively mild course of reactogenicity following the booster vaccination but concurrent with the viral upper respiratory infection, the atopic dermatitis was considered likely related to the infection and unrelated to the investigational vaccine by the investigator.

Head Injury:

One participant with a history of somnambulism, tonsillar hypertrophy, and rhinitis who received the booster vaccination of 120 µg bivalent rLP2086 on Day 1246 after study enrolment. During the 7 days post booster vaccination interval, the participant experienced moderate swelling (10-11 caliper units) and redness (12-13 caliper units) on Days 2 through 4, mild injection site pain on Days 1 through 7, mild to moderate fatigue on Days 1 through 6, and no fever, headache, vomiting, diarrhea, muscle pain or joint pain. The participant was otherwise well until Day 11 post booster vaccination when the participant suffered a mild closed head injury. The participant was evaluated in the emergency room with no abnormalities identified and their condition was considered resolved the same day. The investigator considered the event unrelated to vaccination.

Croup:

No cases of croup with onset 5 days after booster vaccination have been identified in the B1971035 database. The only cases of croup occurring following booster vaccination in the study had onset on Day 34 and Day 165 following vaccination, neither of which were considered related by the investigator. Please clarify which case is being referenced.

Assessment of the MAH's response

The fact that the MAH provided the narratives is appreciated. The assessment of cases is agreed. The MAE of croup occurred at day 165 and had a duration of 5 days.

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

12. Request for supplementary information

12.1. Major objections

Not applicable

12.2. Other concerns

Clinical aspects

1) In total, 63 participants were withdrawn after Visit 8 but before booster vaccination according to the disposition of subjects (Table 1). For these participants who did not continue with the booster vaccination (28.6% of participants in the study), the MAH is asked to determine whether these participants had more/more severe AEs/RRIs during Stage 1 of the study and/or different immune response compared to the participants who did continue and discuss the impact of the observed difference on safety and immunogenicity outcomes, supported by adequate sensitivity analyses for example using multiple imputation.

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

13.1. Major objections

Not applicable

13.2. Other concerns

Clinical aspects

Question 1
In total, 63 participants were withdrawn after Visit 8 but before booster vaccination according to the disposition of subjects (Table 1). For these participants who did not continue with the booster vaccination (28.6% of participants in the study), the MAH is asked to determine whether these participants had more/more severe AEs/RRIs during Stage 1 of the study and/or different immune response compared to the participants who did continue and discuss the impact of the observed difference on safety and immunogenicity outcomes, supported by adequate sensitivity analyses for example using multiple imputation.

Summary of the MAH's response
An analysis was conducted that compared Stage 1 immunogenicity and safety data between the two populations, participants who did not continue with the booster vaccination after Visit 8 and all other participants.

A summary of results is provided below which shows that overall, the safety and immunogenicity data during Stage 1 is generally comparable across the two participant populations.

Immunogenicity

The proportions of participants with hSBA titers ≥ LLOQ for the 4 primary MenB tests trains during Stage 1 by participation continuation status between Visit 8 and booster vaccination are shown in Table 15.

Table 15 Participants With hSBA Titer≥ LLOQ for Primary Strains During Stage 1 by Participation Continuation Status Between Visit 8 and booster Vaccination – Vaccine Groups: 120 µg rLP2086 – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)											
	Participants who Discontinued after Visit 8(6 mo after Vaccination 3) but Before Booster Vaccination				All Other Participants				All Participants			
Strain (Variant) Sampling Time Point	N[a]	n[b]	(%)	(95% CI)[c]	N[a]	n[b]	(%)	(95% CI)[c]	N[a]	n[b]	(%)	(95% CI)[c]
PMB80 (A22)												
Before Vaccination 1	25	0	(0.0)	(0.0, 13.7)	72	3	(4.2)	(0.9, 11.7)	97	3	(3.1)	(0.6, 8.8)
1 Month after Vaccination 2	25	16	(64.0)	(42.5, 82.0)	70	55	(78.6)	(67.1, 87.5)	95	71	(74.7)	(64.8, 83.1)
1 Month after Vaccination 3	25	21	(84.0)	(63.9, 95.5)	71	65	(91.5)	(82.5, 96.8)	96	86	(89.6)	(81.7, 94.9)
6 Months after Vaccination 3	25	3	(12.0)	(2.5, 31.2)	72	9	(12.5)	(5.9, 22.4)	97	12	(12.4)	(6.6, 20.6)
12 Months after Vaccination 3	24	2	(8.3)	(1.0, 27.0)	71	4	(5.6)	(1.6, 13.8)	95	6	(6.3)	(2.4, 13.2)
PMB2001 (A56)												
Before Vaccination 1	25	0	(0.0)	(0.0, 13.7)	70	1	(1.4)	(0.0, 7.7)	95	1	(1.1)	(0.0, 5.7)
1 Month after Vaccination 2	25	25	(100.0)	(86.3, 100.0)	70	70	(100.0)	(94.9, 100.0)	95	95	(100.0)	(96.2, 100.0)
1 Month after Vaccination 3	25	25	(100.0)	(86.3, 100.0)	70	70	(100.0)	(94.9, 100.0)	95	95	(100.0)	(96.2, 100.0)
6 Months after Vaccination 3	23	14	(60.9)	(38.5, 80.3)	65	38	(58.5)	(45.6, 70.6)	88	52	(59.1)	(48.1, 69.5)
12 Months after Vaccination 3	24	11	(45.8)	(25.6, 67.2)	69	25	(36.2)	(25.0, 48.7)	93	36	(38.7)	(28.8, 49.4)
PMB2948 (B24)												
Before Vaccination 1	25	0	(0.0)	(0.0, 13.7)	72	2	(2.8)	(0.3, 9.7)	97	2	(2.1)	(0.3, 7.3)
1 Month after Vaccination 2	25	5	(20.0)	(6.8, 40.7)	61	24	(39.3)	(27.1, 52.7)	86	29	(33.7)	(23.9, 44.7)
1 Month after Vaccination 3	25	17	(68.0)	(46.5, 85.1)	70	51	(72.9)	(60.9, 82.8)	95	68	(71.6)	(61.4, 80.4)
6 Months after Vaccination 3	25	1	(4.0)	(0.1, 20.4)	72	9	(12.5)	(5.9, 22.4)	97	10	(10.3)	(5.1, 18.1)
12 Months after Vaccination 3	23	0	(0.0)	(0.0, 14.8)	70	3	(4.3)	(0.9, 12.0)	93	3	(3.2)	(0.7, 9.1)
PMB2707 (B44)												
Before Vaccination 1	25	0	(0.0)	(0.0, 13.7)	70	1	(1.4)	(0.0, 7.7)	95	1	(1.1)	(0.0, 5.7)
1 Month after Vaccination 2	25	14	(56.0)	(34.9, 75.6)	69	50	(72.5)	(60.4, 82.5)	94	64	(68.1)	(57.7, 77.3)
1 Month after Vaccination 3	25	20	(80.0)	(59.3, 93.2)	69	61	(88.4)	(78.4, 94.9)	94	81	(86.2)	(77.5, 92.4)
6 Months after Vaccination 3	24	11	(45.8)	(25.6, 67.2)	65	25	(38.5)	(26.7, 51.4)	89	36	(40.4)	(30.2, 51.4)
12 Months after Vaccination 3	22	5	(22.7)	(7.8, 45.4)	68	11	(16.2)	(8.4, 27.1)	90	16	(17.8)	(10.5, 27.3)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation.
Note: LLOQ = 1:16 for A22; 1:8 for A56, B24, and B44.
Note: Serology data from 'pre-vaccination' (baseline), 1 month after Vaccination 2 and for '1 month after Vaccination 3' are from the Stage 1 testing campaign.
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 observed proportion of participants, using the Clopper and Pearson method.

Results were comparable between the two populations with no significant differences in proportions of participants with hSBA titers ≥ LLOQ at the timepoints through 12 months after completing the primary vaccination series.

Safety

Reactogenicity - Local Reactions and Systemic Events

The proportions of participants with local reactions or systemic events, by maximum severity, within 7 days after vaccination during Stage 1 by participation continuation status between Visit 8 and booster vaccination are shown in Table 2 in Appendix 2 and Table 3 in Appendix 3.

Some minor point estimate differences in proportions of participants experiencing some reactogenicity events after a particular vaccination in the primary schedule were observed. However, overall and across doses no consistent pattern of reactogenicity being more frequent in the discontinued group was observed. Additionally, the severity of these events was similar between the two populations, and statistical significance of small differences in estimated rates of adverse events (AEs) observed cannot be

established as 95% confidence intervals overlap, either because there was no true difference or more likely, the overall sample size was too small to detect a difference.

Adverse Events

The proportions of participants reporting at least 1 AE during Stage 1 by participation continuation status between Visit 8 and booster vaccination are shown in Table 16.

Table 16 Number (%) of Participants Reporting at Least 1 Adverse Event during Stage 1 Participation Continuation Status Between Visit 8 and Booster Vaccination – Vaccine Groups: 120 µg rLP2086 – Safety Population

		Vaccine Group (as Administered)														
		Participants who Discontinued after Visit 8(6 mo after Vaccination 3) but Before Booster Vaccination					All Other Participants					All Participants				
Analysis Interval	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]	N[a]	n[b]	%	(95% CI[c])	No. of Events[d]
During Vaccination Phase[e]	All AEs	63	52	82.5	(70.9, 90.9)	213	157	102	65.0	(57.0, 72.4)	424	220	154	70.0	(63.5, 76.0)	637
	All SAEs	63	5	7.9	(2.6, 17.6)	6	157	11	7.0	(3.5, 12.2)	15	220	16	7.3	(4.2, 11.5)	21
	All MAEs	63	38	60.3	(47.2, 72.4)	93	157	74	47.1	(39.1, 55.2)	167	220	112	50.9	(44.1, 57.7)	260
	All NDCMCs						157	1	0.6	(0.0, 3.5)	1	220	1	0.5	(0.0, 2.5)	1
During follow-up phase[f]	All AEs	63	21	33.3	(22.0, 46.3)	40	157	53	33.8	(26.4, 41.7)	77	220	74	33.6	(27.4, 40.3)	117
	All SAEs	63	2	3.2	(0.4, 11.0)	2	157	3	1.9	(0.4, 5.5)	3	220	5	2.3	(0.7, 5.2)	5
	All MAEs	63	20	31.7	(20.6, 44.7)	35	157	47	29.9	(22.9, 37.8)	64	220	67	30.5	(24.4, 37.0)	99
Throughout Vaccination Phase and Follow-up Phase[g]	All AEs	63	52	82.5	(70.9, 90.9)	253	157	109	69.4	(61.6, 76.5)	501	220	161	73.2	(66.8, 78.9)	754
	All SAEs	63	5	7.9	(2.6, 17.6)	8	157	14	8.9	(5.0, 14.5)	18	220	19	8.6	(5.3, 13.2)	26
	All MAEs	63	42	66.7	(53.7, 78.0)	128	157	87	55.4	(47.3, 63.3)	231	220	129	58.6	(51.8, 65.2)	359
	All NDCMCs						157	1	0.6	(0.0, 3.5)	1	220	1	0.5	(0.0, 2.5)	1

Abbreviations: MAE = medically attended adverse event; NDCMC = newly diagnosed chronic medical condition.
a. N = number of participants in the specified group. These values are used as the denominators for percentage calculations for the vaccine groups.
b. n = Number of participants reporting at least 1 occurrence of the event specified.
c. Exact 2-sided confidence interval (CI), based on the Clopper and Pearson method.
d. The total number of occurrences of the event specified. Participants can be represented more than once. Event counts are the sum of individual occurrences within that category.
e. Vaccination phase is defined as the time from the first study vaccination [Visit 1] through 1 month after the last study vaccination [Visit 7].
f. Follow-up phase is defined as the time from 1-month after the last study vaccination [Visit 7] through 6 months after the third study vaccination [Visit 8].
g. Throughout Vaccination Phase and Follow-up Phase is from the first study vaccination [Visit 1] through 6 months after the third study vaccination [Visit 8].

Results were generally comparable between the 2 populations and observed point estimate differences were not clinically meaningful. AE and MAE percentages during the Stage 1 vaccination phase trended slightly higher for the population with participants that discontinued after Visit 8. However, this should be interpreted with caution because of the relatively small number of subjects and overlapping confidence intervals, as noted above for reactogenicity. No trend was seen during the follow-up period, and no AEs led to withdrawal between visit 8 and the booster vaccination for any participant.

Conclusion

Upon comparison of immunogenicity and safety data between those who discontinued study participation between Visit 8 and the booster vaccination and those who remained in the study and received the booster dose, no clear differences in proportions experiencing AEs, the severity of those AEs, or immune responses between the two groups were observed. Therefore, the withdrawal of 63 participants between Visit 8 and the booster dose does not appear to be safety related or correlate with immunogenicity trends throughout Stage 1. Pfizer therefore concludes that the immunogenicity and safety data obtained from the subset of participants that received the booster dose is reflective of what was expected of the overall study population dosed at the 120 µg level.

Assessment of the MAH's response
The information provided by the MAH is appreciated.

Based on the immunogenicity data presented, the two groups of participants, those who were withdrawn after Visit 8 but before booster vaccination and the participants who continued, appear similar in their immune response. The difference in proportions of participants with hSBA titers ≥ LLOQ is <10% between the 2 groups after vaccination 3, the last vaccination of the primary series. No trends were observed between the 2 groups with respect to their immune response, which indicates that the withdrawal of the 63 participants, 28.6% of participants, is not expected to impact the immune response after the booster dose.

During the vaccination phase, the percentage of participants experiencing at least 1 AE and MAE was slightly higher in the 63 participants who withdrew compared to the other participants, as 82.5% of participants who withdrew experienced at least 1 AE compared to 65.0% of participants who continued and 60.3% of participants who withdrew experienced an MAE compared to 47.1% of participants who continued.

Based on the information on local reactogenicity, especially after vaccination 3, mild to moderate local reactions (tenderness, redness and swelling) appear to be experienced by more participants who withdrew compared to participants who continued. For systemic events of irritability, drowsiness and loss of or decreased appetite, the participants who withdrew appeared to experience slightly more and slightly more moderate events compared to participants who continued. However, it is agreed with the MAH that the differences are minor. None of the participants or parents/legal guardians claimed to discontinue due to AEs after visit 8.

Overall, there appears to be a slight trend that participants who withdrew experienced slightly more AEs compared to participants who continued during the vaccination phase. However, the severity of the events was mainly mild to moderate, with no increase seen in severe AEs. No difference in SAEs was observed.

Based on the information presented, the slight increase in mild to moderate AEs in the participants who withdrew is considered not to impact the benefit/risk profile of the product for use as a booster vaccine. In addition, the safety profile of the product is not expected to alter; therefore, there is no need to include information on this subset of participants in the SmPC.

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

14. Attachments

1. Product Information (changes highlighted) as adopted by the CHMP on 22-Sep-2022.

Reminders to the MAH

1. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion or 5 days after the submission by the MAH of the final language translations, when there is a linguistic review. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU

2. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant with your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification **within 15 days from adoption of the CHMP Opinion**. The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/en/documents/other/heads-medicines-agencies/european-medicines-agency-guidance-document-identification-commercially-confidential-information_en.pdf

   In addition, should you consider that the CHMP assessment report contains personal data, please provide the EMA Procedure Assistant your proposal for deletion of these data in "track changes" and with detailed justification by 26 November 2021. We would like to remind you that, according to Article 4(1) of Regulation (EU) 2016/679 (General Data Protection Regulation, "GDPR") 'personal data' means any information, relating to an identified or identifiable natural person (the 'data subject'). An identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.

   It is important to clarify that pseudonymised data are also considered personal data. According to Article 4(5) of GDPR pseudonymisation means that personal data is processed in a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information (e.g. key-coded data).

   Accordingly, the name and the patient identification number are two examples of personal data which may relate to an identified or identifiable natural person. The definitions also encompass for instance: office e-mail address or phone number of a company, data concerning health, e.g. information in medical records, clinical reports or case narratives which relates to an identifiable individual."