EMA/331550/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Trumenba

International non-proprietary name: meningococcal group B vaccine (recombinant, adsorbed)

Procedure No. EMEA/H/C/004051/II/0013

Note

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

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List of abbreviations

Abbreviation	Definition
AE	adverse event
bivalent rLP2086	bivalent recombinant lipoprotein 2086 vaccine (Trumenba®)
CFR	case fatality rate
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CRF	case report form
CSR	clinical study report
dTaP/IPV	(low-dose) diphtheria, tetanus, acellular pertussis, and inactivated poliomyelitis virus vaccine
e-diary	electronic diary
EMA	European Medicines Agency
EU	European Union
fHBP	factor H binding protein
GMT	geometric mean titer
HAV	hepatitis A virus (Note: Hepatitis A virus vaccine may be abbreviated as "HAV" in tables and when referring to the vaccine group in text.)
hSBA	serum bactericidal assay using human complement
IMD	invasive meningococcal disease
IRC	internal review committee
ISAP	integrated statistical analysis plan
ISS	integrated summary of safety
LCI	lower bound of 95% confidence interval
LLOQ	lower limit of quantitation
LOD	limit of detection
LP2086	lipoprotein 2086
MAA	Marketing Authorisation Application
MAE	nonserious AE that resulted in an evaluation at a medical facility
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MnB	*Neisseria meningitidis* serogroup B
PIP	Paediatric Investigation Plan
PT	preferred term
RCDC	reverse cumulative distribution curve
rLP2086	recombinant lipoprotein 2086
SAE	serious adverse event
SAP	statistical analysis plan
SBA	serum bactericidal assay
SD	standard deviation
SOC	system organ class
Tdap	tetanus, (low-dose) diphtheria, and (low-dose) acellular pertussis vaccine
UK	United Kingdom
US or USA	United States of America
vs	versus

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Europe MA EEIG submitted to the European Medicines Agency on 28 September 2018 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication for Trumenba to include active immunisation of children 1-9 years old. Sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated in parallel based on the results from the two pivotal studies B1971017 and B1971035. The Package Leaflet is updated in accordance. The RMP version 2.0 has also been submitted.
In addition, the Marketing authorisation holder (MAH) took the opportunity to submit a corrected version of the final report of study B1971016, which was included in the initial marketing authorisation application.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0013/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-001037-PIP-11 was not yet completed as some measures were deferred.

Completion of study B1971035, which is a randomized, controlled, observer-blind trial to describe immunogenicity, safety and tolerability of meningococcal bivalent serogroup B (rLP2086) vaccine for healthy toddlers aged 12 to less than 24 months, is deferred until July 2021.

Furthermore, initiation and completion of study B1971053, which is a dose-finding study to describe the immunogenicity, safety and tolerability of rLP2086 vaccine in healthy infants 2 months of age, is deferred to respectively July 2020 (initiation) and March 2023 (completion).

A waiver was granted for infants from birth to less than 2 months of age based on the grounds that the specific medicinal product is likely to be unsafe and ineffective in this age group.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised

orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	28 September 2018
Start of procedure:	1 December 2018
CHMP Rapporteur Assessment Report	25 January 2019
PRAC Rapporteur Assessment Report	25 January 2019
PRAC members comments	6 February 2019
PRAC Outcome	14 February 2019
CHMP members comments	
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 February 2019
Request for supplementary information (RSI)	28 February 2019
CHMP Rapporteur Assessment Report	26 June 2019
PRAC Rapporteur Assessment Report	26 June 2019
PRAC members comments	3 July 2019
PRAC Outcome	11 July 2019
CHMP members comments	15 July 2019
Updated CHMP Rapporteur Assessment Report	18 July 2019
Request for supplementary information (RSI)	25 July 2019
CHMP Rapporteur Assessment Report	29 October 2019
CHMP members comments	
Updated CHMP Rapporteur Assessment Report	8 November 2019
Request for supplementary information (RSI)	14 November 2019
CHMP Rapporteur Assessment Report	2 March 2020
CHMP members comments	16 March 2020
Request for supplementary information (RSI)	26 March 2020
CHMP Rapporteur Assessment Report	8 May 2020
CHMP members comments	18 May 2020
Updated CHMP Rapporteur Assessment Report	20 May 2020
Opinion	28 May 2020

1.3. Steps taken for the re-examination procedure

N/A

2. Scientific discussion

2.1. Introduction

Trumenba is intended 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 to extend the indication to include a wider paediatric population starting from 1 year of age for Trumenba and to include relevant information in the labelling.

This variation includes submission of the CSRs on two randomised, open label, controlled, multicentre, primary vaccination studies to evaluate the safety and immunogenicity of Trumenba given as 3 doses to in children aged 12 to <24 months (B1971035) and children aged ≥24 months to <10 years (B1971017). In addition, the MAH submitted an integrated analysis of safety and immunogenicity.

Study B1971017 has been submitted by the MAH in an art. 46 submission on 1 September 2017.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1. Design of Controlled Studies in Children 1 to 9 Years of Age Providing the Basis for the Proposed Age Expansion to 1 Year in this Clinical Overview

Study ID Phase/Purpose	Subject Age (Years)[a]	Number of Subjects Vaccinated With Bivalent rLP2086 or Control Vaccine	Region	Design and Dosage Schedule
B1971017 Phase 2/Safety & immunogenicity	≥2 to <10	400 (294 rLP2086; 106 control) 120 μg rLP2086 (n=294) HAV/saline (n=106)	EU	Randomized, active-controlled, observer-blinded study -120 μg rLP2086 at 0, 2, and 6 months -HAV at 0 and 6 months; saline at 2 months
B1971035 Phase 2/Safety & immunogenicity	≥1 to <2	396 (264 rLP2086; 132 control) 60 μg rLP2086 (n=44) 120 μg rLP2086 (n=220) HAV/saline (n=132)	EU/ Aus	Randomized, active-controlled, observer-blinded, sponsor-unblinded study -60 or 120 μg rLP2086 at 0, 2, and 6 months -HAV at 0 and 6 months; saline at 2 months In Stage 2, subjects who received rLP2086 will continue to be followed for antibody persistence through 48 months after the last study dose. Note: The primary clinical study report (immunogenicity data through 1 month following the third dose and safety data through 6 months following the third dose) has been completed and these data are included in the Type II variation.

Abbreviations: Aus=Australia; EU=European Union; HAV=hepatitis A virus vaccine; n=number of subjects; rLP2086= bivalent recombinant lipoprotein 2086 vaccine.

a. Age at enrollment; subjects could have aged beyond the enrollment age for subsequent injections.
Source: Summary of Clinical Safety, Table 2.

2.4. Clinical efficacy

2.4.1. Main studies

The application is based on two clinical studies B1971017 and B1971035.

Study B1971035 is newly submitted, 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 the primary vaccination and stage 2, which assesses the duration of the immune response and the response to a booster dose. The first stage of the study was designed to assess the immunogenicity, safety, and tolerability of bivalent rLP2086 when administered as a 3-dose primary series at Months 0, 2, and 6. Children in the control group received two doses of hepatitis A vaccine and

one dose of saline in order to maintain the blind. The study was conducted between August 2015 and August 2017 at 26 centres in four countries (Australia, Czech Republic, Finland and Poland) in accordance with GCP.

Only data from stage 1 are contained within the current submission. The MAH intends to submit the persistence and booster data from stage 2 of this study in the third quarter of 2020.

B1971017 is a Phase 2, randomized, controlled, observer-blinded study to describe the immunogenicity, safety, and tolerability of bivalent rLP2086 in healthy subjects aged ≥24 months to <10 years. This study has been assessed within context of an Art 46 submission, that assessment is included in this current AR and issues relevant for the extension of indication will be highlighted.

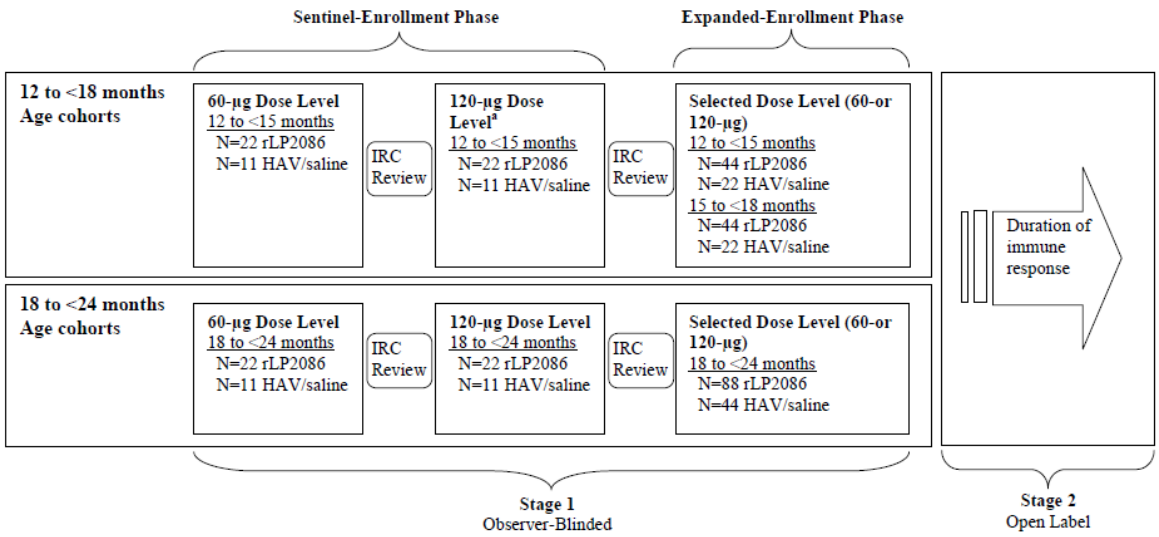
Study B1971035

Methods

Overall Study Plan

The study design is depicted in figure 1 below.

Figure 1. Study Design



Stage 1 consists of the primary vaccination stage and includes a sentinel enrolment phase in which a half dose of the vaccine (60 µg) was used evaluated in two cohorts including children aged 12 to <15 months and 18 to <24 months of age before moving to a full dose of the vaccine (120 µg) in the same age cohorts. Once the safety was established in this sentinel enrolment phase, the expanded-enrolment phase was started which evaluated the 120 µg dose in children aged 12 to <18 months of age and 18 to <24 months of age. Selection of dose level for the expanded-enrolment phase was based on an internal review committee (IRC) review of the safety profile of the 2 dose levels.

The current submission includes data from Stage 1 of the study. Subjects participated in Stage 1 of the study for up to 18 months. For immunogenicity, all data through 1 month after Vaccination 3 (Visit 7) are presented with the exception of secondary MnB test strain data supporting an exploratory objective. For

safety, all data through 6 months after Vaccination 3 (Visit 8) are presented. Immunogenicity results from blood draws performed beyond 1 month after the third dose are not included.

Study participants

Children in the ages of 12-<15 months or 18-<25 months could be enrolled in the sentinel cohort, children aged 12-<24 months could be enrolled in the expanded drug cohort.

Exclusion criteria included previous vaccination with MnB or HAV vaccine, contraindications to HAV vaccine, conditions associated with prolonged bleeding time that would contraindicate intramuscular injection, forms of immune suppression, history of *N. meningitidis* or *gonorrhoeae,* significant neurological disorders or neuroinflammatory conditions, a history of seizures, a previous anaphylactic reaction to any vaccine or vaccine-related component, chronic use of antibiotics, receipt of blood products. Furthermore, in and exclusion criteria common for vaccine trials in children were in place.

Objectives

Primary 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 1 month after the third vaccination with bivalent rLP2086, in healthy toddlers aged 12 to <18 months at study entry.
- 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, in healthy toddlers aged 18 to <24 months at study entry.

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.

Secondary objectives

These included the measurement of the immune response as measured by hSBA for both age strata combined, as well as the immune response hSBA at different time points (6, 12, 24, 36, and 48 months after the third vaccination and one month after the second vaccination).

Exploratory objectives included aimed at further describing the immune response at different timepoints in both age strata and strata combined against the four primary MnB strains and against secondary MnB strains.

Treatments

Bivalent rLP2086 (60 µg or 120 µg) was administered as an intramuscular injection into either the deltoid muscle or anterolateral thigh muscle 3 times over the course of the study: the first vaccination at Visit 1 (Month 0), second vaccination at Visit 4 (Month 2), and third vaccination at Visit 6 (Month 6).

HAV vaccine (at Months 0 and 6) was chosen as the control in this study. In comparison to other recommended vaccines for this age group, HAV vaccine has a better tolerability profile. In addition, HAV vaccine confers a benefit to subjects who might be at increased risk for hepatitis A viral infection either

during future travel or during other exposures. The generally recommended regimen for HAV vaccine is 2 doses at Months 0 and 6. In this study, saline was given at Month 2 to maintain the study blind.

Outcomes/endpoints

The primary immunogenicity endpoints were:

- Proportions of subjects achieving an hSBA titre ≥ lower limit of quantitation (LLOQ) 1 month after the third vaccination, for each of the 4 primary MnB test strains in healthy toddlers 12 to <18 months of age at study entry.
- Proportions of subjects achieving an hSBA titre ≥LLOQ 1 month after the third vaccination, for each of the 4 primary MnB test strains in healthy toddlers 18 to <24 months of age at study entry.

Secondary immunogenicity endpoints
(note, only immunogenicity endpoints applicable to Visits 1 to 7 (Vaccination 1 to 3 months after Vaccination 3) are available at this time)
For both age strata combined:

- 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.

For both age strata separately and in both age strata combined:

- Proportions of subjects with hSBA titres ≥ LLOQ for each of the 4 primary MnB test strains at 1 month after the second vaccination with bivalent rLP2086 and 6, 12, 24, 36, and 48 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 at each applicable blood sampling visit.
- hSBA geometric mean titres (GMTs) for each of the 4 primary MnB test strains at each applicable blood sampling visit.

In addition there were several exploratory endpoints, including proportions with hSBA ≥ different cut-off values and GMTs at each blood sampling visit, proportions with a four fold increase, response by baseline titre (< or ≥ Limit of Detection (LOD)), and response for those who had the response against all four primary strains tested as well as those with responses against secondary strains measured.

Laboratory assays and time-points
Blood draws for endpoints included in this submission were performed:

- Before Vaccination 1 (Visit 1);
- One (1) month after Vaccination 2 (Visit 5);
- One (1) month after Vaccination 3 (Visit 7);

Note that there will be a follow up of the immune response up to four years after primary vaccination.

Four (4) primary MnB test strains, PMB80 (A22), PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44), each expressing a factor H binding protein (fHBP) variant heterologous to the vaccine component antigens, were used in the hSBAs for determination of the immunogenicity endpoints in this study.

The LLOQ was 1:16 for PMB80 (A22), 1:8 for PMB2001 (A56), 1:8 for PMB2707 (B44), and 1:8 for PMB2948 (B24). For the calculation of GMTs, hSBA results below the LLOQ were set to 0.5 × LLOQ for the primary analysis.

Once all subjects completed enrolment (Visit 1), the independent statistical centre (ISC), a statistical team not involved in the conduct of the study, provided 2 subject listings (randomly selected, 50% of

subjects to be tested for PMB80 [A22]/PMB2948 [B24] and the remaining 50% of subjects to be tested for PMB2001 [A56]/PMB2707 [B44]) to the sponsor's sample management team. Both listings followed the same randomization ratio (2:1) and age-strata distribution as in the study design. The same strain pair (PMB80 [A22]/PMB2948 [B24] or PMB2001 [A56]/PMB2707 [B44]) was tested across all visits for the same subjects.

Once testing for the primary analyses was completed, and if sufficient volume of sera was available, additional testing to assess the immune response to bivalent rLP2086 could be considered as follows: PMB80 (A22) and PMB2948 (B24) could be tested in serum samples from the 50% of subjects who received bivalent rLP2086 and whose serum samples were originally tested for PMB2001 (A56) and PMB2707 (B44). Conversely, PMB2001 (A56) and PMB2707 (B44) could be tested in serum samples from the 50% of subjects who received bivalent rLP2086 and were originally tested for PMB80 (A22) and PMB2948 (B24). Testing for secondary strains could be performed. None of these additional assays were performed for this primary analysis CSR.

Sample size

Approximately 396 subjects were planned to be enrolled in this study. The study sample size was not based on hypothesis testing. However, using a 1-sided exact test for 1-sample binomial population, with an alpha level of 5% (2-sided), with a true response rate of 65%, 88 evaluable subjects could provide about 80% power to detect at least a 50% response rate for 1 strain. Under the same conditions, 176 subjects could provide about 98% power to detect at least a 50% response rate for 1 strain. Assuming that 20% of subjects are not evaluable, about 88 or 176 subjects would be available for immunogenicity analysis if 110 or 220 subjects were enrolled in the selected dose/age stratum.

Randomisation

396 healthy toddlers stratified by age, 12 to <18 months or 18 to <24 months old, were randomly assigned in a 2:1 ratio to receive bivalent rLP2086 (either of 2 dose levels [60 µg or 120 µg]) or a licensed paediatric HAV vaccine (0.5 mL)/sterile saline solution for injection (0.5-mL of 0.85% sodium chloride).
Allocation of subjects to vaccine groups was through an interactive response technology system.

Blinding (masking)

The study was observer blinded. All immunogenicity assays were performed by blinded laboratory staff.

Statistical methods

Analysis sets
The primary analyses of immunogenicity were based on the defined *evaluable immunogenicity population.*
To be included in the evaluable immunogenicity population, subjects had to meet all the following criteria:

1. Were eligible for the study (through 1 month after Vaccination 3).
2. Had been randomized to a study group.
3. Had received scheduled investigational products as randomized.
4. Had pre-vaccination blood drawn prior to the first vaccination dose and had post-Vaccination 3 blood draw (Visit 7) within 28 to 42 days after the third vaccination (Visit 6).
5. Had a valid and determinate assay result for the proposed analysis.
6. Had received no prohibited vaccines or treatment.
7. Had no other major protocol violations as determined by the sponsor's global medical monitor.

The *modified Intent-to-Treat Population* (mITT) included all randomized subjects who had at least 1 valid and determinate assay result related to a proposed analysis.
The *safety population* was used for all safety analyses. The safety population included all subjects who received at least 1 dose of an investigational product (bivalent rLP2086, HAV vaccine, or saline) and for whom safety data were available. For the safety analysis, subjects were analysed according to the investigational product received.

Analysis
This was not a hypothesis-testing study; thus, an estimation approach was used to assess the primary, secondary, and exploratory objectives in this study.

Analysis of Primary Endpoints
The primary analysis for the primary objectives was the proportion of subjects with an hSBA titre ≥LLOQ 1 month after the third vaccination, for each of the 4 primary MnB test strains in healthy toddlers aged 12 to <18 months, and 18 to <24 months, at study entry respectively. The evaluable immunogenicity population was used for this summary and both percentages and confidence intervals (CIs) are displayed.

Analysis of Secondary Endpoints
All of the analyses performed on the mITT population were considered as secondary analyses.
Analyses for secondary endpoints also included percent of subjects with hSBA titres ≥ LLOQ for each of the 4 primary MnB test strains 1 month following the third vaccination for both the evaluable immunogenicity population and for the mITT population.

Assessing Missing hSBA With Other Variables
All of the subjects, for the combined age strata, were dichotomized to 2 categories: missing hSBA or non-missing hSBA. If a subject was missing data at any blood sampling visit up to 1 month after Vaccination 3 (Month 7) for any of the 2 selected strains, the subject was categorized as 'Missing (1)'; if the subject had hSBA results for all blood sampling visits up to 1 month after Vaccination 3 (Month 7) for the 2 selected primary strains, the subject was categorized as 'Nonmissing (0)'. Summary statistics were provided for the following variables by the missing indicator: age, sex, centre, vaccine group, and GMT for each strain for each group at each visit.

A mixed-effect model with repeated measurement will be utilized to assess the effect of race, centre and gender, in which both baseline and the post-vaccination titres up until Month 7 (in logarithmic scale) are modelled as dependent variables for each primary strain.

This model is using maximum likelihood estimation; therefore, it also serves as a sensitivity analyses on missing data for the GMT. To account for the intra-subject correlation among the repeated measures, an unstructured covariance matrix will be used. In case the model does not converge, further covariance structures will be explored (ie, First-order autoregressive, compound symmetry). 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. 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.

Results

Participant flow

In total, 396 subjects 12 to <24 months of age were randomized in this study. Of the subjects randomized, a total of 44 subjects received 60 µg of bivalent rLP2086, 220 subjects received 120 µg of bivalent rLP2086, and 132 subjects received HAV vaccine/saline.

Of the 396 subjects randomised, 385 subjects (97.2%) completed the vaccination phase and 348 (87.9%) were included in the primary evaluable immunogenicity population. Most of the exclusions were due to missing scheduled prevaccination or postvaccination blood drawn (31, 7.8%), due to receiving prohibited vaccines or treatment (16, 4.0%), or due to lack of adherence to the vaccination (11, 2.8%) or not being eligible for the study (13, 3.3%).

Recruitment

The first subject was enrolled 31 August 2015 and the last study visit was on 21 August 2017.
Most (152) of the 396 subjects were enrolled in Poland followed by 118 in Australia, 100 in Czech Republic and in 26 in Finland.

Conduct of the study

There were 2 amendments to the original protocol dated 16 June 2014 (03 February 2015, 19 April 2016).

Baseline data

The mean age of the subjects in the primary evaluable immunogenicity population was 17.3 months (range 12 to 23 months; median 17.5 months) with an equal balance male/female.

Table 2. Demographic Characteristics – Safety Population

	Vaccine Group (as Administered)							
	60 µg rLP2086		120 µg rLP2086		HAV/Saline		Total	
	n[a]	(%)	n[a]	(%)	n[a]	(%)	n[a]	(%)
Administered[b]								
12 to <24 Months	44		220		132		396	
12 to <18 Months	22		110		66		198	
18 to <24 Months	22		110		66		198	
Sex								
Male								
12 to <24 Months	23	(52.3)	106	(48.2)	58	(43.9)	187	(47.2)
12 to <18 Months	9	(40.9)	53	(48.2)	25	(37.9)	87	(43.9)
18 to <24 Months	14	(63.6)	53	(48.2)	33	(50.0)	100	(50.5)
Female								
12 to <24 Months	21	(47.7)	114	(51.8)	74	(56.1)	209	(52.8)
12 to <18 Months	13	(59.1)	57	(51.8)	41	(62.1)	111	(56.1)
18 to <24 Months	8	(36.4)	57	(51.8)	33	(50.0)	98	(49.5)
Race								
White								
12 to <24 Months	37	(84.1)	210	(95.5)	127	(96.2)	374	(94.4)
12 to <18 Months	20	(90.9)	106	(96.4)	62	(93.9)	188	(94.9)
18 to <24 Months	17	(77.3)	104	(94.5)	65	(98.5)	186	(93.9)
Asian								
12 to <24 Months	5	(11.4)	2	(0.9)	1	(0.8)	8	(2.0)
12 to <18 Months	2	(9.1)	1	(0.9)	0	(0.0)	3	(1.5)
18 to <24 Months	3	(13.6)	1	(0.9)	1	(1.5)	5	(2.5)
Other[c]								
12 to <24 Months	2	(4.5)	8	(3.6)	4	(3.0)	14	(3.5)
12 to <18 Months	0	(0.0)	3	(2.7)	4	(6.1)	7	(3.5)
18 to <24 Months	2	(9.1)	5	(4.5)	0	(0.0)	7	(3.5)
Ethnicity								

Hispanic/Latino								
12 to <24 Months	0	(0.0)	2	(0.9)	0	(0.0)	2	(0.5)
12 to <18 Months	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.5)
18 to <24 Months	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.5)
Non-Hispanic/non-Latino								
12 to <24 Months	44	(100.0)	218	(99.1)	132	(100.0)	394	(99.5)
12 to <18 Months	22	(100.0)	109	(99.1)	66	(100.0)	197	(99.5)
18 to <24 Months	22	(100.0)	109	(99.1)	66	(100.0)	197	(99.5)
Country								
Australia								
12 to <24 Months	15	(34.1)	69	(31.4)	34	(25.8)	118	(29.8)
12 to <18 Months	3	(13.6)	32	(29.1)	16	(24.2)	51	(25.8)
18 to <24 Months	12	(54.5)	37	(33.6)	18	(27.3)	67	(33.8)
Czech Republic								
12 to <24 Months	22	(50.0)	39	(17.7)	39	(29.5)	100	(25.3)
12 to <18 Months	12	(54.5)	17	(15.5)	19	(28.8)	48	(24.2)
18 to <24 Months	10	(45.5)	22	(20.0)	20	(30.3)	52	(26.3)
Finland								
12 to <24 Months	0	(0.0)	17	(7.7)	9	(6.8)	26	(6.6)
12 to <18 Months	0	(0.0)	17	(15.5)	9	(13.6)	26	(13.1)
18 to <24 Months	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Poland								
12 to <24 Months	7	(15.9)	95	(43.2)	50	(37.9)	152	(38.4)
12 to <18 Months	7	(31.8)	44	(40.0)	22	(33.3)	73	(36.9)
18 to <24 Months	0	(0.0)	51	(46.4)	28	(42.4)	79	(39.9)
Age at first vaccination (months)								
12 to <24 Months								
n	44		220		132		396	
Mean (SD)	16.9 (4.08)		17.4 (3.54)		17.3 (3.58)		17.3 (3.61)	
Median	16.5		17.5		17.5		17.5	
Min, max	12, 23		12, 23		12, 23		12, 23	
12 to <18 Months								
n	22		110		66		198	
Mean (SD)	13.0 (1.00)		14.2 (1.51)		14.1 (1.77)		14.1 (1.59)	
Median	13.0		14.0		14.0		14.0	
Min, max	12, 15		12, 17		12, 17		12, 17	
18 to <24 Months								
n	22		110		66		198	
Mean (SD)	20.7 (1.62)		20.5 (1.70)		20.4 (1.55)		20.5 (1.63)	
Median	21.0		21.0		20.0		20.0	
Min, max	18, 23		18, 23		18, 23		18, 23	

a. n = Number of subjects with the specified characteristic.
b. The values in this section are used as the denominators for the percentage calculations by age strata.
c. Other = any race other than white, black, or Asian; however, no black subjects enrolled in the study.
Program ID: Study B1971035/CP CS_DEMO.SAS. Date of Reporting Dataset Creation: 26SEP2017. Runtime ID: 12OCT2017 10:05. File ID: 1_5_CS_DEMO_SAF.HTM.

Numbers analysed

Of the 396 subjects randomised, 385 subjects (97.2%) completed the vaccination phase and 348 (87.9%) were included in the primary evaluable immunogenicity population. Forty-eight (12.1%) subjects were excluded from the evaluable immunogenicity population. Most of the exclusions were due to missing scheduled prevaccination or postvaccination blood drawn (31, 7.8%), due to receiving prohibited vaccines or treatment (16, 4.0%), or due to lack of adherence to the vaccination (11, 2.8%) or not being eligible for the study (13, 3.3%).

The **modified Intent-to-Treat Population** included 396 randomized subjects. **The safety population** included all 396 randomised persons.

Outcomes and estimation

Primary Outcome

Proportion of Subjects Achieving an hSBA Titre ≥ LLOQ

The response in both age strata separately as well the age strata combined per vaccine group against each of the primary test strains 1 month after vaccination 3 is presented in the following table 3.

Table 3. Subjects With hSBA Titre ≥ LLOQ for Primary Strains one month after Vaccination 3 – Evaluable Immunogenicity Population

	12 to <18 months (n/N) % (95% CI)		18 to <24 months (n/N) % (95% CI)		12 to <24 months (n/N) % (95% CI)	
	60µg	120µg	60µg	120µg	60µg	120µg
PMB80 (A22)	8/9	41/45	10/11	45/51	18/20	86/96
	88.9% (51.8, 99.7)	91.1% (78.8, 97.5)	90.9% (58.7, 99.8)	88.2% (76.1, 95.6)	90.0% (68.3, 98.8)	89.6% (81.7, 94.9)
PMB2001 (A56)	9/9	47/47	10/10	48/48	19/19	95/95
	100.0% (66.4, 100.0)	100.0% (92.5, 100.0)	100.0% (69.2, 100.0)	100.0% (92.6, 100.0)	100.0% (82.4, 100.0)	100.0% (96.2, 100.0)
PMB2948 (B24)	8/9	32/45	9/11	36/50	17/20	68/95
	88.9% (51.8, 99.7)	71.1% (55.7, 83.6)	81.8% (48.2, 97.7)	72.0% (57.5, 83.8)	85.0% (62.1, 96.8)	71.6% (61.4, 80.4)
PMB2707 (B44)	17/19	41/47	9/10	40/47	17/19	81/94
	88.9% (51.8, 99.7)	87.2% (74.3, 95.2)	90.0% (55.5, 99.7)	85.1% (71.7, 93.8)	89.5% (66.9, 98.7)	86.2% (77.5, 92.4)

The proportion of subjects in the HAV/saline group achieving an hSBA titre ≥ LLOQ did not change over time compared to baseline and varied from 0 to 3 (5%) subjects per stratum (data not shown in this AR).

Results for the mITT population were similar to those of the evaluable immunogenicity population (data not shown in this AR).

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.

Secondary Outcomes

Proportion of Subjects Achieving an hSBA Titre ≥ LLOQ

The response in both age strata separately as well the age strata combined per vaccine group against each of the primary test strains 1 month after vaccination 2 is presented in the following table 4.

Table 4. Subjects With hSBA Titre ≥ LLOQ for Primary Strains one month after Vaccination 2 – Evaluable Immunogenicity Population

	12 to <18 months (n/N) % (95% CI)		18 to <24 months (n/N) % (95% CI)		12 to <24 months (n/N) % (95% CI)	
	60µg	120µg	60µg	120µg	60µg	120µg
PMB80 (A22)	9/10	29 / 45	6/9	42/50	15 / 19	71/95
	90.0% (55.5, 99.7)	64.4% (48.8, 78.1)	66.7% (29.9, 92.5)	84.0% (70.9, 92.8)	78.9% (54.4, 93.9)	74.7% (64.8, 83.1)
PMB2001 (A56)	9/9	47/47	9/10	48/48	18/19	95/95
	100.0% (66.4, 100.0)	100.0% (92.5, 100.0)	90.0% (55.5, 99.7)	100.0% (92.6, 100.0)	94.7% (74.0, 99.9)	100.0% (96.2, 100.0)

PMB2948 (B24)	7/10	10/42	4/9	19/44	11/19	29/86
	70.0% (34.8, 93.3)	23.8% (12.1, 39.5)	44.4% (13.7, 78.8)	43.2% (28.3, 59.0)	57.9% (33.5, 79.7)	33.7% (23.9, 44.7)
PMB2707 (B44)	7/9	34/47	6/10	30/47	13/19	64/94
	77.8% (40.0, 97.2)	72.3% (57.7, 77.3)	60.0% (26.2, 87.8)	63.8% (57.7, 77.3)	68.4% (43.4, 87.4)	68.1% (57.7, 77.3)

hSBA GMTs

For the combined age stratum, the hSBA GMTs at baseline were 8.0 and 8.4 for PMB80 (A22); 4.0 and 4.1 for PMB2001 (A56); 4.4 and 4.1 for PMB2948 (B24); and 4.0 and 4.0 for PMB2707 (B44) for the 60-µg and 120-µg groups, respectively. The hSBA GMTs one month after vaccination 2 and vaccination 3 per vaccination group and age strata are presented in the following tables 5 and 6.

Table 5. GMTs for Primary Strains one month after Vaccination 2 – Evaluable Immunogenicity Population

	12 to <18 months (n) GMT (95% CI)		18 to <24 months (n) GMT (95% CI)		12 to <24 months (n) GMT (95% CI)	
	60µg	120µg	60µg	120µg	60µg	120µg
PMB80 (A22)	10	45	9	50	19	95
	42.2 (22.6, 79.1)	24.6 (17.8, 34.2)	23.5 (10.1, 54.9)	36.8 (26.9, 50.3)	32.0 (19.7, 52.0)	30.4 (24.3, 38.1)
PMB2001 (A56)	9	47	10	48	19	95
	101.6 (64.0, 161.2)	117.2 (89.7, 153.0)	68.6 (28.2, 166.8)	104.6 (80.4, 136.0)	82.6 (51.4, 132.9)	110.6 (92.0, 133.0)
PMB2948 (B24)	10	42	9	44	19	86
	10.6 (6.2, 18.0)	6.0 (4.7, 7.8)	6.9 (4.1, 11.5	8.5 (6.4, 11.3)	8.6 (6.1, 12.2)	7.2 (5.9, 8.7)
PMB2707 (B44)	9	47	10	47	19	94
	23.5 (9.3, 59.4)	22.1 (15.5, 31.6)	21.1 (6.5, 68.3)	17.0 (11.8, 24.4)	22.2 (11.2, 43.9)	19.4 (15.1, 24.9)

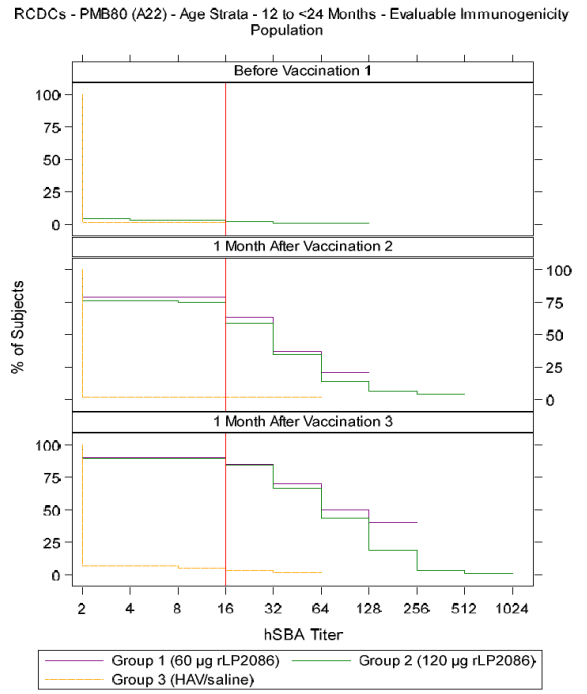
Table 6. GMTs for Primary Strains one month after Vaccination 3 – Evaluable Immunogenicity Population

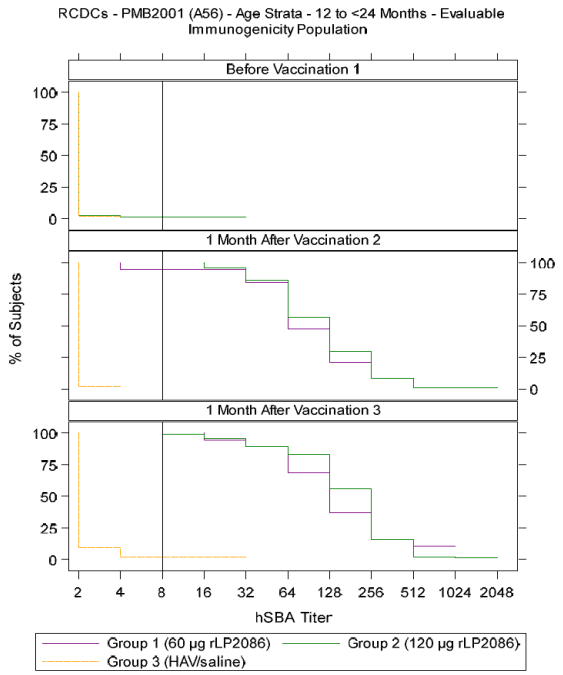
	12 to <18 months (n) GMT (95% CI)		18 to <24 months (n) GMT (95% CI)		12 to <24 months (n) GMT (95% CI)	
	60µg	120µg	60µg	120µg	60µg	120µg
PMB80 (A22)	9	45	11	51	20	96
	80.6 (30.9,210.7)	63.0 (44.5, 89.3)	82.3 (36.5, 185.8)	71.4 (52.7, 96.6)	81.6 (46.6, 142.8)	67.3 (53.7, 84.3)
PMB2001 (A56)	9	47	10	48	19	95
	109.7 (70.4, 171.1)	190.6 (146.9,247.4)	181.0 (68.6, 477.9)	154.4 (116.3,205.1)	142.8 (85.5, 238.6)	171.4 (141.6,207.4)

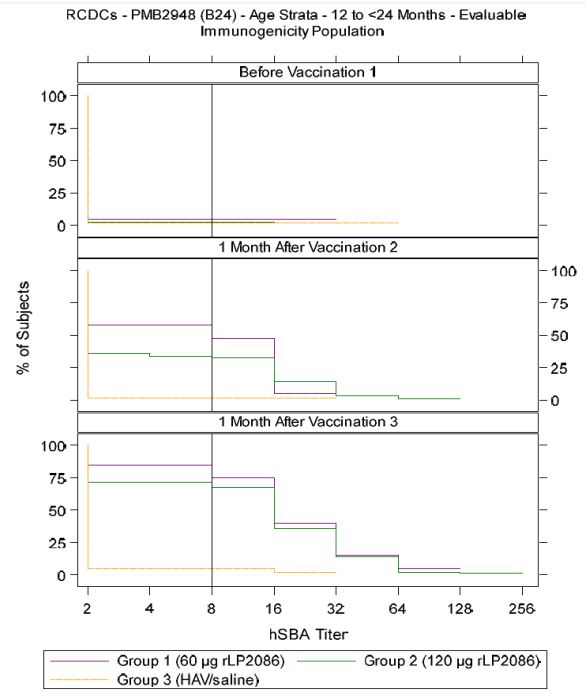
PMB2948 (B24)	9	45	11	50	20	95
	20.2 (11.1, 36.6)	15.8 (11.4, 21.8)	17.0 (8.2, 35.5)	14.5 (11.1, 19.1)	18.4 (11.8, 28.6)	15.1 (12.3, 18.6)
PMB2707 (B44)	9	47	10	47	19	94
	29.6 (11.6, 75.8)	46.3 (31.6, 67.8)	34.3 (15.0, 78.2)	44.9 (31.3, 64.5)	32.0 (18.3, 55.8)	45.6 (35.2, 59.0)

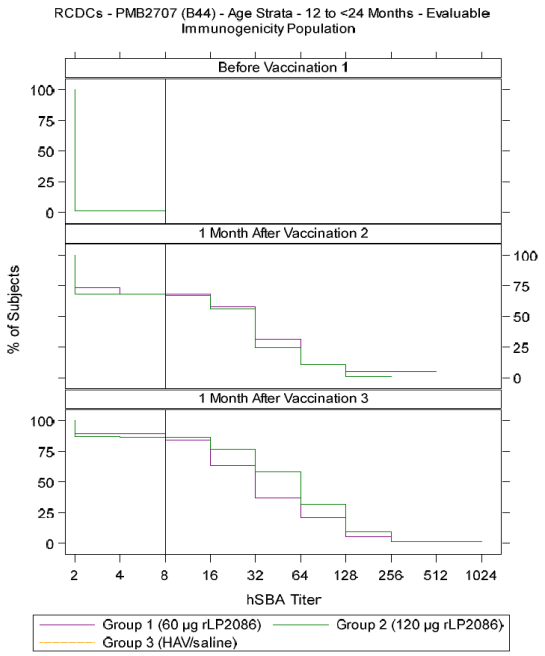
Reverse cumulative distribution curves

The Reverse Cumulative Distribution Curves for the combined age strata (12 to <24 Months, Evaluable Immunogenicity Population) for all four primary strains are shown in the figures below.









Study B1971017

Methods

Overall Study Plan

This was a Phase 2, randomized, controlled, observer-blinded, multicentre study designed to assess the immunogenicity, safety, and tolerability of bivalent rLP2086 at the 120-µg dose level administered to healthy subjects aged ≥24 months to <10 years as part of a Month 0, 2, and 6 schedule. See table 7 below for details.

Table 7. Study design

	Vaccination 1	Post-Vaccination 1 Follow-up	Vaccination 2	Post-Vaccination 2 Blood Draw	Vaccination 3	Post-Vaccination 3 Blood Draw	Month 12 Follow-up and Blood Draw
Visit	1	2	3	4	5	6	7
Approximate month	0	1	2	3	6	7	12
Group 1 (300 subjects)	Bivalent rLP2086		Bivalent rLP2086		Bivalent rLP2086		
Group 2 (100 subjects)	HAV vaccine		Saline		HAV vaccine		
Blood draw (all subjects)	5-10 mL			5-10 mL		5-10 mL	5-10 mL

HAV = hepatitis A virus
Source: B1971017 Protocol Amendment 1 Table 1

Study participants

Subjects were eligible to enter the study if they were healthy subjects aged ≥24 months and <10 years at the time of randomization and complied to the standard inclusion criteria in vaccine trials.

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

- Previous vaccination with any meningococcal serogroup B vaccine or HAV vaccination.
- Subjects who were receiving any allergen immunotherapy with an unlicensed product or subjects who were receiving allergen immunotherapy with a licensed product and who were not on stable maintenance doses.
- A known or suspected defect of the immune system that would have prevented an immune response to the vaccine, such as subjects with congenital or acquired defects in B-cell function, those receiving chronic systemic (oral, intravenous, or intramuscular) corticosteroid therapy, or those receiving immunosuppressive therapy. Subjects with terminal complement deficiency could be included.
- History of microbiologically proven disease caused by *N meningitidis* or *Neisseria gonorrhoeae*.
- Significant neurological disorder or history of seizure (excluding simple febrile seizure).
- Any neuroinflammatory or autoimmune condition, including but not limited to transverse myelitis, uveitis, optic neuritis, and multiple sclerosis.
- Receipt of any blood products, including immunoglobulin (Ig), within 6 months before the first study vaccination.
- Current chronic use of systemic antibiotics.

Objectives

Primary Immunogenicity Objectives:

- To describe the immune response as measured by serum bactericidal assay using human complement (hSBA) performed with 4 primary *Neisseria meningitidis* serogroup B (MnB) test 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, in healthy subjects aged ≥24 months to <4 years at study entry.
- To describe the immune response as measured by hSBA performed with 4 primary MnB test strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, measured 1 month after the third vaccination with bivalent rLP2086, in healthy subjects aged ≥4 years to <10 years at study entry.

Primary Safety Objective: To evaluate the safety profile of bivalent rLP2086 compared to a control (hepatitis A virus [HAV] vaccine).

Secondary Objectives:

- To describe the immune response as measured by hSBA performed with 4 primary MnB test strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, measured 1 month after the third vaccination with bivalent rLP2086, in healthy subjects aged ≥24 months to <10 years at study entry (ie, in the combined age stratum).
- To describe the immune response as measured by hSBA performed with 4 primary MnB test strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, measured 1 month after the second vaccination and 6 months after the third vaccination with bivalent rLP2086, in healthy subjects aged ≥24 months to <4 years at study entry, in healthy subjects aged ≥4 years to <10 years at study entry, and in the combined age stratum.

Exploratory Objectives: The immune response was further described through additional endpoints, as measured by hSBA performed with 4 primary MnB test strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, at specified time points, in healthy subjects aged ≥24 months to <4 years at study entry, in healthy subjects aged ≥4 years to <10 years at study entry, and in the combined age stratum.

Treatments

Subjects in Group 1 were administered bivalent rLP2086 by intramuscular injection into the upper deltoid muscle of the arm at Months 0, 2, and 6. Subjects in Group 2 were administered HAV vaccine/saline/HAV vaccine into the upper deltoid muscle of the arm at Months 0, 2, and 6, respectively.
HAV vaccine administered at Months 0 and 6 was chosen as the control in this study so that subjects randomized to the control group would receive a direct benefit from participating in the study, as the HAV vaccine is not a required immunization in either Poland or Finland and most subjects would therefore not have received it prior to enrolment. HAV vaccine has a well-established safety and tolerability profile and provides protection to subjects who may become at increased risk for hepatitis A infection either during travel or other exposures. The generally recommended regimen by the US CDC and the European CDC for HAV vaccine is 2 doses at Months 0 and 6. In this study, saline was given at Month 2 to maintain the study blind.

Outcomes/endpoints

For the primary analyses, 2 of the primary test strains (PMB80 [A22] and PMB2948 [B24]) were tested at each blood sampling time point for half of the subjects (in both groups), and the other 2 primary test strains (PMB2001 [A56] and PMB2707 [B44]) were tested at each blood sampling time point for the remaining half of the subjects.

The primary immunogenicity endpoints were:

- Proportion of subjects aged ≥24 months to <4 years (at study entry) with hSBA titre ≥ lower limit of quantitation (LLOQ)1 for each of the 4 primary MnB test strains 1 month after the third vaccination with bivalent rLP2086.
- Proportion of subjects aged ≥4 years to <10 years (at study entry) with hSBA titre ≥LLOQ for each of the 4 primary MnB test strains 1 month after the third vaccination with bivalent rLP2086.

The secondary immunogenicity endpoints were:

- In healthy subjects aged ≥24 months to <10 years at study entry:
    - Proportion of subjects with hSBA titre ≥LLOQ for each of the 4 primary MnB test strains 1 month after the third vaccination with bivalent rLP2086.
- In healthy subjects aged ≥24 months to <4 years at study entry, in healthy subjects aged ≥4 years to <10 years at study entry, and in the combined age stratum:
    - Proportion of subjects with hSBA titre ≥LLOQ for each of the 4 primary MnB test strains 1 month after the second vaccination and 1 and 6 months after the third vaccination with bivalent rLP2086.
    - hSBA GMTs for each of the 4 primary test strains at baseline, 1 month after the second vaccination, and 1 and 6 months after the third vaccination with bivalent rLP2086.
    - Proportions of subjects achieving hSBA titres of ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the 4 primary test strains at baseline, 1 month after the second vaccination, and 1 and 6 months after the third vaccination with bivalent rLP2086.

Sample size

The study sample size was not based on hypothesis-testing criteria. Approximately 400 subjects were planned to be randomly assigned to one of the two groups in a 3:1 ratio.

Randomisation

Randomisation was stratified according to age to ensure that equal numbers of subjects were included in the ≥24-month to <4-year age stratum and the ≥4-year to <10-year age stratum.

Allocation of subjects to vaccine groups proceeded through the use of an interactive response technology (IRT) system that was accessible 24 hours a day, 365 days a year. Having logged in, the site personnel (study coordinator or specified designee) were required to enter or select certain information including, but not limited to, the user's identification (ID).

[1] The LLOQ was 1:16 for PMB80 (A22), 1:8 for PMB2001 (A56), 1:8 for PMB2707 (B44), and 1:8 for PMB2948 (B24).

Blinding (masking)

The study was observer blinded.

Statistical methods

There were no hypotheses testing for immunogenicity analysis. An estimation approach was used to assess the primary, secondary, and exploratory objectives. All of the binary endpoints (including primary endpoints) were summarized with 2-sided 95% CIs using the exact method. Geometric mean titre (GMTs) on hSBA results were also summarized with 95% CIs.

The following analysis populations were defined:

(primary analysis population) included all subjects who were:

1. Randomized into the study;
2. Were eligible, ie, satisfied all inclusion/exclusion criteria, through 1 month after Vaccination 3;
3. Received all the scheduled investigational products at Visits 1, 3, and 5 as randomized;
4. Had baseline blood drawn prior to the first dose of vaccine and had the post-Vaccination 3 blood draw (Visit 6) within 28 to 42 days after Vaccination 3 (Visit 5). The interval day was calculated as the blood draw date minus the vaccination date;
5. Had valid and determinate assay results for the proposed analysis; and
6. Had no important protocol deviations

- Modified intent-to-treat (mITT) population: All randomized subjects who had at least 1 valid and determinate assay result related to a proposed analysis
- Safety population: All subjects who received at least 1 dose of the investigational product (bivalent rLP2086, HAV vaccine, or saline) and with safety data available were included in the safety population.

Subgroup Analyses

The following immunogenicity and safety endpoints were descriptively summarized by race (white, black, Asian, and other), by sex (male, female), and by country:

- Proportion of subjects with hSBA titre ≥ LLOQ for each of the 4 primary MnB test strains at each time point,
- GMTs for each of the 4 primary MnB test strains at each time point,
- Primary safety endpoints related to reactogenicity, AEs, SAEs, and MAEs.

For the calculation of GMTs, hSBA results below the LLOQ were set as 0.5 × LLOQ for the primary analysis. Additionally, a sensitivity analysis using a mixed-effects model with repeated measures (MMRM) could have been applied to the primary endpoints. The MMRM was to use the maximum likelihood estimation, and it was under the assumption that the data were missing at random (MAR). As <50% of the subjects had 2 strains tested and the remaining subjects had the other 2 strains tested, no sensitivity analyses were performed, as per Section 7.1 of the SAP (Section 16.1.9).

Results

Participant flow

Table 8. Disposition of All Subjects – Safety Population

	Vaccine Group (as Administered)					
	Group 1 rLP2086		Group 2 HAV/Saline		Total	
	n[a]	(%)	n[a]	(%)	n[a]	(%)
Randomized[b]						
≥24 Months to <10 years	294		106		400	
≥24 Months to <4 years	145		55		200	
≥4 Years to <10 years	149		51		200	
Withdrawn before vaccination						
≥24 Months to <10 years	0	(0.0)	0	(0.0)	0	(0.0)
≥24 Months to <4 years	0	(0.0)	0	(0.0)	0	(0.0)
≥4 Years to <10 years	0	(0.0)	0	(0.0)	0	(0.0)
Vaccinated						
≥24 Months to <10 years	294		106		400	
≥24 Months to <4 years	145		55		200	
≥4 Years to <10 years	149		51		200	
Vaccination 1						
≥24 Months to <10 years	294	(100.0)	106	(100.0)	400	(100.0)
≥24 Months to <4 years	145	(100.0)	55	(100.0)	200	(100.0)
≥4 Years to <10 years	149	(100.0)	51	(100.0)	200	(100.0)
Vaccination 2						
≥24 Months to <10 years	291	(99.0)	104	(98.1)	395	(98.8)
≥24 Months to <4 years	143	(98.6)	54	(98.2)	197	(98.5)
≥4 Years to <10 years	148	(99.3)	50	(98.0)	198	(99.0)
Vaccination 3						
≥24 Months to <10 years	287	(97.6)	104	(98.1)	391	(97.8)
≥24 Months to <4 years	140	(96.6)	54	(98.2)	194	(97.0)
≥4 Years to <10 years	147	(98.7)	50	(98.0)	197	(98.5)
Vaccination phase						
Completed						
≥24 Months to <10 years	286	(97.3)	104	(98.1)	390	(97.5)
≥24 Months to <4 years	140	(96.6)	54	(98.2)	194	(97.0)
≥4 Years to <10 years	146	(98.0)	50	(98.0)	196	(98.0)
Withdrawn						
≥24 Months to <10 years	8	(2.7)	2	(1.9)	10	(2.5)
≥24 Months to <4 years	5	(3.4)	1	(1.8)	6	(3.0)
≥4 Years to <10 years	3	(2.0)	1	(2.0)	4	(2.0)
Reason for withdrawal during vaccination phase						
Adverse event						
≥24 Months to <10 years	2	(0.7)	1	(0.9)	3	(0.8)
≥24 Months to <4 years	2	(1.4)	0	(0.0)	2	(1.0)
≥4 Years to <10 years	0	(0.0)	1	(2.0)	1	(0.5)
Withdrew consent						
≥24 Months to <10 years	2	(0.7)	1	(0.9)	3	(0.8)
≥24 Months to <4 years	1	(0.7)	1	(1.8)	2	(1.0)
≥4 Years to <10 years	1	(0.7)	0	(0.0)	1	(0.5)
No longer meets eligibility criteria						
≥24 Months to <10 years	2	(0.7)	0	(0.0)	2	(0.5)
≥24 Months to <4 years	1	(0.7)	0	(0.0)	1	(0.5)
≥4 Years to <10 years	1	(0.7)	0	(0.0)	1	(0.5)

	Vaccine Group (as Administered)					
	Group 1 rLP2086		Group 2 HAV/Saline		Total	
	n[a]	(%)	n[a]	(%)	n[a]	(%)
Lost to follow-up						
≥24 Months to <10 years	1	(0.3)	0	(0.0)	1	(0.3)
≥24 Months to <4 years	1	(0.7)	0	(0.0)	1	(0.5)
No longer willing to participate in study						
≥24 Months to <10 years	1	(0.3)	0	(0.0)	1	(0.3)
≥4 Years to <10 years	1	(0.7)	0	(0.0)	1	(0.5)
Study						
Completed						
≥24 Months to <10 years	283	(96.3)	104	(98.1)	387	(96.8)
≥24 Months to <4 years	137	(94.5)	54	(98.2)	191	(95.5)
≥4 Years to <10 years	146	(98.0)	50	(98.0)	196	(98.0)
Withdrawn						
≥24 Months to <10 years	3	(1.0)	0	(0.0)	3	(0.8)
≥24 Months to <4 years	3	(2.1)	0	(0.0)	3	(1.5)
Reason for withdrawal						
Withdrew consent						
≥24 Months to <10 years	3	(1.0)	0	(0.0)	3	(0.8)
≥24 Months to <4 years	3	(2.1)	0	(0.0)	3	(1.5)
Completed 6-month follow-up						
≥24 Months to <10 years	283	(96.3)	104	(98.1)	387	(96.8)
≥24 Months to <4 years	137	(94.5)	54	(98.2)	191	(95.5)
≥4 Years to <10 years	146	(98.0)	50	(98.0)	196	(98.0)
Completed all study visits (Visit 1 to Visit 7)						
≥24 Months to <10 years	283	(96.3)	104	(98.1)	387	(96.8)
≥24 Months to <4 years	137	(94.5)	54	(98.2)	191	(95.5)
≥4 Years to <10 years	146	(98.0)	50	(98.0)	196	(98.0)
Completed all study procedures						
≥24 Months to <10 years	276	(93.9)	99	(93.4)	375	(93.8)
≥24 Months to <4 years	134	(92.4)	52	(94.5)	186	(93.0)
≥4 Years to <10 years	142	(95.3)	47	(92.2)	189	(94.5)

a. n = Number of subjects with the specified characteristic.
b. The values in this section are used as the denominators for the percentage calculations by age strata.
Program ID: Study B1971017/CP CS_DISP.SAS. Date of Reporting Dataset Creation: 01JUN2017. Runtime ID: 16JUN2017 11:22. File ID: T_1_2_CS_DISP.HTM.

Recruitment

Relevant recruitment dates are:

- First Subject First Visit: 27 August 2015
- Last Subject Last Visit: 01 March 2017
- Serology Completion Date: 23 May 2017

There were 14 sites included in this study. Six sites were in Finland, 8 sites were in Poland.

Conduct of the study

There was 1 amendment to the original protocol dated 12 May 2014. All subjects were enrolled under Amendment 1 of the protocol dated 03 February 2015.

- Updated the description of the control HAV vaccine.
- Updated the introduction with current information.
- Clarified that investigational product was to be administered to subjects who were blinded.

Baseline data

Overall, 52% of subjects were female, and the majority of the subjects were white (98.8%) and non-Hispanic/non-Latino (100.0%). The mean age (SD) at first vaccination was 4.3 (2.21) years (range of 2 to 9 years). Demographic characteristics were similar between groups and age strata. See table 9 below.

Table 9. Demographic characteristics – evaluable immunogenicity population

	Vaccine Group (as Randomized) Group 1 rLP2086 n[a] (%)	Group 2 HAV/Saline n[a] (%)	Total n[a] (%)
Randomized[b]			
≥24 Months to <10 years	274	97	371
≥24 Months to <4 years	136	52	188
≥4 Years to <10 years	138	45	183
Sex			
Female			
≥24 Months to <10 years	138 (50.4)	58 (59.8)	196 (52.8)
≥24 Months to <4 years	68 (50.0)	33 (63.5)	101 (53.7)
≥4 Years to <10 years	70 (50.7)	25 (55.6)	95 (51.9)
Male			
≥24 Months to <10 years	136 (49.6)	39 (40.2)	175 (47.2)
≥24 Months to <4 years	68 (50.0)	19 (36.5)	87 (46.3)
≥4 Years to <10 years	68 (49.3)	20 (44.4)	88 (48.1)
Race			
White			
≥24 Months to <10 years	272 (99.3)	95 (97.9)	367 (98.9)
≥24 Months to <4 years	136 (100.0)	51 (98.1)	187 (99.5)
≥4 Years to <10 years	136 (98.6)	44 (97.8)	180 (98.4)
Other			
≥24 Months to <10 years	2 (0.7)	2 (2.1)	4 (1.1)
≥24 Months to <4 years	0 (0.0)	1 (1.9)	1 (0.5)
≥4 Years to <10 years	2 (1.4)	1 (2.2)	3 (1.6)
Ethnicity			
Non-Hispanic/non-Latino			
≥24 Months to <10 years	274 (100.0)	97 (100.0)	371 (100.0)
≥24 Months to <4 years	136 (100.0)	52 (100.0)	188 (100.0)
≥4 Years to <10 years	138 (100.0)	45 (100.0)	183 (100.0)
Country			
Finland			
≥24 Months to <10 years	106 (38.7)	35 (36.1)	141 (38.0)
≥24 Months to <4 years	40 (29.4)	16 (30.8)	56 (29.8)
≥4 Years to <10 years	66 (47.8)	19 (42.2)	85 (46.4)
Poland			
≥24 Months to <10 years	168 (61.3)	62 (63.9)	230 (62.0)
≥24 Months to <4 years	96 (70.6)	36 (69.2)	132 (70.2)
≥4 Years to <10 years	72 (52.2)	26 (57.8)	98 (53.6)
Age at randomization (years)			
≥24 Months to <10 years			
n	274	97	371
Mean (SD)	4.3 (2.24)	4.2 (2.22)	4.3 (2.23)
Median	4.0	3.0	3.0
Min, max	2, 9	2, 9	2, 9

Numbers analysed

A total of 400 subjects aged ≥24 months to <10 years were randomized in this study. Of the subjects randomized, 294 subjects were in Group 1 (bivalent rLP2086) and 106 subjects were in Group 2 (HAV/saline). There were 200 subjects randomized in each of the ≥24-month to <4-year and ≥4-year to <10-year age strata.

Overall, a total of 375 (93.8%) subjects completed all study procedures and completion was similar in each age strata. A total of 371 (92.8%) subjects were included in the evaluable immunogenicity population, and 29 (7.3%) subjects were excluded from the evaluable immunogenicity population. All 400

randomized subjects were included in the mITT population. Subjects could have been excluded from the immunogenicity populations for more than 1 reason. A total of 21 (5.3%) subjects were excluded from the evaluable immunogenicity population because they did not have baseline blood drawn prior to the first dose of vaccine or after Vaccination 3, 15 (3.8%) subjects did not have a valid and determinate assay result at any visit, 11 (2.8%) subjects were not eligible or became ineligible for the study before or at the 1-month post-Vaccination 3 visit, 11 (2.8%) subjects did not receive vaccine as randomized at all vaccination visits, and 4 (1.0%) subjects had an important protocol deviation as identified by the medical monitor. Overall, the 2 study groups and 2 age strata were comparable with respect to the percentages of subjects who were excluded from the evaluable immunogenicity population.

Outcomes and estimation

Primary and Secondary Endpoints

The proportion of subjects in each age stratum with an hSBA titre ≥LLOQ for each of the 4 primary MnB test strains is presented in Table 10 below for the evaluable immunogenicity population at different timepoints.

Table 10. Subjects With hSBA Titre ≥ LLOQ for Primary Strains – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)							
	Group 1 rLP2086				Group 2 HAV/Saline			
Strain (Variant) Sampling Time Point Age Strata	N[a]	n[b]	(%)	(95% CI)[c]	N[a]	n[b]	(%)	(95% CI)[c]
PMB80 (A22)								
Before Vaccination 1								
≥24 Months to <10 years	134	12	(9.0)	(4.7, 15.1)	47	3	(6.4)	(1.3, 17.5)
≥24 Months to <4 years	68	3	(4.4)	(0.9, 12.4)	26	1	(3.8)	(0.1, 19.6)
≥4 Years to <10 years	66	9	(13.6)	(6.4, 24.3)	21	2	(9.5)	(1.2, 30.4)
1 Month after Vaccination 2								
≥24 Months to <10 years	130	90	(69.2)	(60.5, 77.0)	45	2	(4.4)	(0.5, 15.1)
≥24 Months to <4 years	64	38	(59.4)	(46.4, 71.5)	24	0	(0.0)	(0.0, 14.2)
≥4 Years to <10 years	66	52	(78.8)	(67.0, 87.9)	21	2	(9.5)	(1.2, 30.4)
1 Month after Vaccination 3								
≥24 Months to <10 years	135	118	(87.4)	(80.6, 92.5)	45	3	(6.7)	(1.4, 18.3)
≥24 Months to <4 years	68	57	(83.8)	(72.9, 91.6)	25	1	(4.0)	(0.1, 20.4)
≥4 Years to <10 years	67	61	(91.0)	(81.5, 96.6)	20	2	(10.0)	(1.2, 31.7)
6 Months after Vaccination 3								
≥24 Months to <10 years	126	41	(32.5)	(24.5, 41.5)	47	4	(8.5)	(2.4, 20.4)
≥24 Months to <4 years	63	12	(19.0)	(10.2, 30.9)	26	2	(7.7)	(0.9, 25.1)
≥4 Years to <10 years	63	29	(46.0)	(33.4, 59.1)	21	2	(9.5)	(1.2, 30.4)
PMB2001 (A56)								
Before Vaccination 1								
≥24 Months to <10 years	132	11	(8.3)	(4.2, 14.4)	47	7	(14.9)	(6.2, 28.3)
≥24 Months to <4 years	67	1	(1.5)	(0.0, 8.0)	24	2	(8.3)	(1.0, 27.0)
≥4 Years to <10 years	65	10	(15.4)	(7.6, 26.5)	23	5	(21.7)	(7.5, 43.7)
1 Month after Vaccination 2								
≥24 Months to <10 years	133	133	(100.0)	(97.3, 100.0)	43	7	(16.3)	(6.8, 30.7)
≥24 Months to <4 years	66	66	(100.0)	(94.6, 100.0)	21	2	(9.5)	(1.2, 30.4)
≥4 Years to <10 years	67	67	(100.0)	(94.6, 100.0)	22	5	(22.7)	(7.8, 45.4)
1 Month after Vaccination 3								
≥24 Months to <10 years	139	139	(100.0)	(97.4, 100.0)	43	9	(20.9)	(10.0, 36.0)
≥24 Months to <4 years	68	68	(100.0)	(94.7, 100.0)	24	1	(4.2)	(0.1, 21.1)
≥4 Years to <10 years	71	71	(100.0)	(94.9, 100.0)	19	8	(42.1)	(20.3, 66.5)
6 Months after Vaccination 3								
≥24 Months to <10 years	131	108	(82.4)	(74.8, 88.5)	46	9	(19.6)	(9.4, 33.9)
≥24 Months to <4 years	61	49	(80.3)	(68.2, 89.4)	24	4	(16.7)	(4.7, 37.4)
≥4 Years to <10 years	70	59	(84.3)	(73.6, 91.9)	22	5	(22.7)	(7.8, 45.4)
PMB2948 (B24)								
Before Vaccination 1								
≥24 Months to <10 years	134	7	(5.2)	(2.1, 10.5)	47	2	(4.3)	(0.5, 14.5)
≥24 Months to <4 years	67	2	(3.0)	(0.4, 10.4)	26	1	(3.8)	(0.1, 19.6)
≥4 Years to <10 years	67	5	(7.5)	(2.5, 16.6)	21	1	(4.8)	(0.1, 23.8)
1 Month after Vaccination 2								
≥24 Months to <10 years	128	73	(57.0)	(48.0, 65.7)	45	4	(8.9)	(2.5, 21.2)
≥24 Months to <4 years	65	32	(49.2)	(36.6, 61.9)	24	2	(8.3)	(1.0, 27.0)
≥4 Years to <10 years	63	41	(65.1)	(52.0, 76.7)	21	2	(9.5)	(1.2, 30.4)
1 Month after Vaccination 3								

Strain (Variant) / Sampling Time Point / Age Strata	Vaccine Group (as Randomized) Group 1 rLP2086 N[a]	n[b]	(%)	(95% CI)[c]	Group 2 HAV/Saline N[a]	n[b]	(%)	(95% CI)[c]
≥24 Months to <10 years	126	112	(88.9)	(82.1, 93.8)	46	2	(4.3)	(0.5, 14.8)
≥24 Months to <4 years	63	54	(85.7)	(74.6, 93.3)	26	2	(7.7)	(0.9, 25.1)
≥4 Years to <10 years	63	58	(92.1)	(82.4, 97.4)	20	0	(0.0)	(0.0, 16.8)
6 Months after Vaccination 3								
≥24 Months to <10 years	129	20	(15.5)	(9.7, 22.9)	47	0	(0.0)	(0.0, 7.5)
≥24 Months to <4 years	65	6	(9.2)	(3.5, 19.0)	26	0	(0.0)	(0.0, 13.2)
≥4 Years to <10 years	64	14	(21.9)	(12.5, 34.0)	21	0	(0.0)	(0.0, 16.1)
PMB2707 (B44)								
Before Vaccination 1								
≥24 Months to <10 years	138	0	(0.0)	(0.0, 2.6)	50	0	(0.0)	(0.0, 7.1)
≥24 Months to <4 years	67	0	(0.0)	(0.0, 5.4)	26	0	(0.0)	(0.0, 13.2)
≥4 Years to <10 years	71	0	(0.0)	(0.0, 5.1)	24	0	(0.0)	(0.0, 14.2)
1 Month after Vaccination 2								
≥24 Months to <10 years	130	63	(48.5)	(39.6, 57.4)	50	0	(0.0)	(0.0, 7.1)
≥24 Months to <4 years	63	36	(57.1)	(44.0, 69.5)	26	0	(0.0)	(0.0, 13.2)
≥4 Years to <10 years	67	27	(40.3)	(28.5, 53.0)	24	0	(0.0)	(0.0, 14.2)
1 Month after Vaccination 3								
≥24 Months to <10 years	134	106	(79.1)	(71.2, 85.6)	50	0	(0.0)	(0.0, 7.1)
≥24 Months to <4 years	65	52	(80.0)	(68.2, 88.9)	26	0	(0.0)	(0.0, 13.2)
≥4 Years to <10 years	69	54	(78.3)	(66.7, 87.3)	24	0	(0.0)	(0.0, 14.2)
6 Months after Vaccination 3								
≥24 Months to <10 years	135	14	(10.4)	(5.8, 16.8)	49	0	(0.0)	(0.0, 7.3)
≥24 Months to <4 years	66	8	(12.1)	(5.4, 22.5)	26	0	(0.0)	(0.0, 13.2)
≥4 Years to <10 years	69	6	(8.7)	(3.3, 18.0)	23	0	(0.0)	(0.0, 14.8)

Abbreviation: 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.
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 observed proportion of subjects, using the Clopper and Pearson method.
Program ID: Study B1971017/CP IMM_LLOQ.SAS. Date of Reporting Dataset Creation: 01JUN2017. Runtime ID: 16JUN2017 11:22. File ID: T_2_2_IMM_LLOQ_EVL.HTM.

Proportion of Subjects Achieving an hSBA Titre ≥ LLOQ for each of the 4 primary MnB test strains 1 month after the third vaccination with bivalent rLP2086.

The proportion of subjects aged ≥24 months to <4 years and ≥4 years to <10 years in Group 1 with an hSBA titre ≥ LLOQ at 1 month after the third vaccination was 83.8% and 91.0%, respectively, for PMB80 (A22); 100.0% for both age strata for PMB2001 (A56); 85.7% and 92.1%, respectively, for PMB2948 (B24); and 80.0% and 78.3%, respectively, for PMB2707 (B44).

Immunopersistence: Proportion of Subjects Achieving hSBA Titre ≥ LLOQ 6 Months After Third Vaccination

In general, there was a decline in the proportion of subjects with an hSBA titre ≥LLOQ for each of the 4 primary MnB test strains observed among Group 1 subjects in both age strata at 6 months after the third vaccination.

For subjects aged ≥24 months to <4 years, from 1 month after the third vaccination to 6 months after the third vaccination, the proportion of subjects with an hSBA titre ≥LLOQ decreased from 83.8% to 19.0%, respectively, for PMB80 (A22); 100.0% to 80.3%, respectively, for PMB2001 (A56); 85.7% to 9.2%, respectively for PMB2948 (B24); and 80.0% to 12.1%, respectively, for PMB2707 (B44). For subjects aged ≥4 years to <10 years, from 1 month after the third vaccination to 6 months after the third vaccination, the proportion of subjects with an hSBA titre ≥ LLOQ decreased from 91.0% to 46.0%, respectively, for PMB80 (A22); 100.0% to 84.3%, respectively, for PMB2001 (A56); 92.1% to 21.9%, respectively for PMB2948 (B24); and 78.3% to 8.7%, respectively, for PMB2707 (B44).

hSBA GMTs

Table 11 provides hSBA GMTs for the 4 primary MnB strains for the evaluable immunogenicity population.

Table 11. hSBA GMTs for Primary Strains – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)					
	Group 1 rLP2086			Group 2 HAV/Saline		
Strain (Variant) Sampling Time Point Age Strata	N[a]	GMT[b]	(95% CI)[c]	N[a]	GMT[b]	(95% CI)[c]
PMB80 (A22)						
Before Vaccination 1						
≥24 Months to <10 years	134	8.7	(8.3, 9.1)	47	8.9	(7.8, 10.1)
≥24 Months to <4 years	68	8.3	(7.9, 8.8)	26	8.2	(7.8, 8.7)
≥4 Years to <10 years	66	9.1	(8.3, 9.9)	21	9.8	(7.2, 13.2)
1 Month after Vaccination 2						
≥24 Months to <10 years	130	20.1	(17.4, 23.2)	45	8.6	(7.7, 9.7)
≥24 Months to <4 years	64	17.4	(14.2, 21.4)	24	8.0	(NE, NE)
≥4 Years to <10 years	66	23.1	(18.9, 28.3)	21	9.4	(7.4, 12.0)
1 Month after Vaccination 3						
≥24 Months to <10 years	135	35.8	(30.5, 42.2)	45	8.8	(7.8, 9.8)
≥24 Months to <4 years	68	33.7	(26.4, 42.9)	25	8.7	(7.3, 10.3)
≥4 Years to <10 years	67	38.2	(30.6, 47.6)	20	8.9	(7.6, 10.4)
6 Months after Vaccination 3						
≥24 Months to <10 years	126	12.4	(10.9, 14.2)	47	8.7	(7.9, 9.7)
≥24 Months to <4 years	63	10.9	(9.0, 13.1)	26	8.4	(7.8, 9.1)
≥4 Years to <10 years	63	14.2	(11.8, 17.0)	21	9.1	(7.4, 11.3)
PMB2001 (A56)						
Before Vaccination 1						
≥24 Months to <10 years	132	4.9	(4.3, 5.5)	47	5.6	(4.4, 7.2)
≥24 Months to <4 years	67	4.1	(3.9, 4.3)	24	4.9	(3.7, 6.6)
≥4 Years to <10 years	65	5.8	(4.6, 7.3)	23	6.5	(4.3, 9.8)
1 Month after Vaccination 2						
≥24 Months to <10 years	133	96.6	(83.0, 112.5)	43	5.8	(4.4, 7.6)
≥24 Months to <4 years	66	103.8	(84.2, 127.9)	21	5.0	(3.6, 7.1)
≥4 Years to <10 years	67	90.0	(71.9, 112.7)	22	6.6	(4.2, 10.5)
1 Month after Vaccination 3						
≥24 Months to <10 years	139	183.3	(156.7, 214.4)	43	6.0	(4.6, 7.7)
≥24 Months to <4 years	68	175.6	(139.1, 221.6)	24	4.5	(3.5, 5.7)
≥4 Years to <10 years	71	191.0	(153.9, 237.1)	19	8.6	(5.4, 13.8)
6 Months after Vaccination 3						
≥24 Months to <10 years	131	31.3	(25.3, 38.7)	46	6.0	(4.6, 7.8)
≥24 Months to <4 years	61	27.0	(19.7, 36.9)	24	6.0	(4.0, 8.9)
≥4 Years to <10 years	70	35.7	(26.6, 47.8)	22	6.0	(4.2, 8.7)
PMB2948 (B24)						
Before Vaccination 1						
≥24 Months to <10 years	134	4.5	(4.1, 4.9)	47	4.4	(3.9, 4.9)
≥24 Months to <4 years	67	4.3	(3.8, 4.9)	26	4.3	(3.7, 5.1)
≥4 Years to <10 years	67	4.6	(4.0, 5.2)	21	4.4	(3.6, 5.4)
1 Month after Vaccination 2						
≥24 Months to <10 years	128	11.1	(9.2, 13.5)	45	4.8	(4.0, 5.8)
≥24 Months to <4 years	65	9.1	(7.0, 11.9)	24	4.8	(3.7, 6.2)
≥4 Years to <10 years	63	13.7	(10.3, 18.2)	21	4.9	(3.6, 6.6)
1 Month after Vaccination 3						
≥24 Months to <10 years	126	22.6	(19.1, 26.8)	46	4.3	(3.9, 4.8)
≥24 Months to <4 years	63	19.1	(14.9, 24.5)	26	4.6	(3.8, 5.6)
≥4 Years to <10 years	63	26.8	(21.3, 33.9)	20	4.0	(NE, NE)

Strain (Variant) Sampling Time Point Age Strata	Vaccine Group (as Randomized) Group 1 rLP2086 N[a]	GMT[b]	(95% CI)[c]	Group 2 HAV/Saline N[a]	GMT[b]	(95% CI)[c]
6 Months after Vaccination 3						
≥24 Months to <10 years	129	5.6	(4.8, 6.5)	47	4.0	(NE, NE)
≥24 Months to <4 years	65	5.1	(4.1, 6.3)	26	4.0	(NE, NE)
≥4 Years to <10 years	64	6.2	(4.9, 7.7)	21	4.0	(NE, NE)
PMB2707 (B44)						
Before Vaccination 1						
≥24 Months to <10 years	138	4.0	(NE, NE)	50	4.0	(NE, NE)
≥24 Months to <4 years	67	4.0	(NE, NE)	26	4.0	(NE, NE)
≥4 Years to <10 years	71	4.0	(NE, NE)	24	4.0	(NE, NE)
1 Month after Vaccination 2						
≥24 Months to <10 years	130	11.7	(9.3, 14.7)	50	4.0	(NE, NE)
≥24 Months to <4 years	63	17.1	(11.8, 24.8)	26	4.0	(NE, NE)
≥4 Years to <10 years	67	8.2	(6.3, 10.6)	24	4.0	(NE, NE)
1 Month after Vaccination 3						
≥24 Months to <10 years	134	39.8	(30.6, 51.6)	50	4.0	(NE, NE)
≥24 Months to <4 years	65	43.6	(29.9, 63.6)	26	4.0	(NE, NE)
≥4 Years to <10 years	69	36.5	(25.2, 52.7)	24	4.0	(NE, NE)
6 Months after Vaccination 3						
≥24 Months to <10 years	135	5.1	(4.4, 5.9)	49	4.0	(NE, NE)
≥24 Months to <4 years	66	5.2	(4.2, 6.4)	26	4.0	(NE, NE)
≥4 Years to <10 years	69	5.0	(4.1, 6.2)	23	4.0	(NE, NE)

Abbreviations: GMT = geometric mean titer; hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; NE = not estimable.
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.
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 back transformations of confidence levels based on the Student t distribution for the mean logarithm of the hSBA titers.
Program ID: Study B1971017/CP IMM_GMT.SAS. Date of Reporting Dataset Creation: 01JUN2017. Runtime ID: 16JUN2017 11:22. File ID: T_2_9_IMM_GMT_EVL.HTM.

Defined hSBA Titres

Subjects who achieved an hSBA titre ≥1:4 and ≥1:16 are described below.

The proportion of subjects aged ≥24 months to <4 years, and ≥4 years to <10 years, in Group 1 with an hSBA titre ≥1:4 at baseline was 5.9% and 19.7%, respectively, for PMB80 (A22); 3.0% and 18.5%, respectively, for PMB2001 (A56); 4.5% and 9.0%, respectively, for PMB2948 (B24); and 0.0% and 1.4%, respectively for PMB2707 (B44). Subjects aged ≥24 months to <4 years, and ≥4 years to <10 years, in Group 1 with an hSBA titre ≥1:16 at baseline was 4.4% and 13.6%, respectively, for PMB80 (A22); 1.5% and 15.4%, respectively, for PMB2001 (A56); 3.0% and 6.0%, respectively, for PMB2948 (B24); and 0.0% for both age strata for PMB2707 (B44).

The proportion of Group 1 subjects in the combined age stratum with an hSBA titre ≥1:4 and ≥1:16 at 1 month after the second vaccination was 74.6% and 69.2%, respectively, for PMB80 (A22); 100.0% and 99.2%, respectively, for PMB2001 (A56); 60.9% and 50.8%, respectively, for PMB2948 (B24); and 57.7% and 43.1%, respectively, for PMB2707 (B44).

The proportion of subjects aged ≥24 months to <4 years, and ≥4 years to <10 years, in Group 1 with an hSBA titre ≥1:4 at 1 month after the third vaccination was 86.8% and 98.5%, respectively, for PMB80 (A22); 100.0% for each age strata for PMB2001 (A56); 90.5% and 95.2% for PMB2948 (B24); and 81.5% and 82.6%, respectively for PMB2707 (B44). Subjects aged ≥24 months to <4 years, and ≥4 years to <10 years, in Group 1 with an hSBA titre ≥1:16 at 1 month after the third vaccination was 83.8% and 91.0%, respectively, for PMB80 (A22); 100.0% for each age stratum for PMB2001 (A56);

81.0% and 88.9%, respectively, for PMB2948 (B24); and 81.5% to 82.6% and 80.0% and 75.4%, respectively, for PMB2707 (B44).

The proportion of Group 1 subjects in the combined age stratum with an hSBA titre ≥1:4 and ≥1:16 at 1 month after the third vaccination was 92.6% and 87.4%, respectively, for PMB80 (A22); 100.0% and 100.0%, respectively, for PMB2001 (A56); 92.9% and 84.9%, respectively, for PMB2948 (B24); and 82.1% and 77.6%, respectively, for PMB2707 (B44).

Overall, there was a decrease observed in the proportion of Group 1 subjects in both age strata who achieved defined hSBA titres from 1 month after the third vaccination to 6 months after the third vaccination.

For Group 1 subjects aged ≥24 months to <4 years and aged ≥4 years to <10 years, from 1 month after the third vaccination to 6 months after the third vaccination, the proportion of subjects with an hSBA titre ≥1:4 decreased from 86.8% to 25.4% and 98.5% to 55.6%, respectively, for PMB80 (A22); 100.0% to 82.0% and 100.0% to 85.7%, respectively for PMB2001 (A56); 90.5% to 13.8% and 95.2% to 26.6%, respectively, for PMB2948 (B24); and 81.5% to 13.6% and 82.6% to 13.0%, respectively, for PMB2707 (B44).

For Group 1 subjects in the combined age stratum, from 1 month after the third vaccination to 6 months after the third vaccination, the proportion of subjects with an hSBA titre ≥1:4 decreased from 92.6% to 40.5% for PMB80 (A22); 100.0% to 84.0% for PMB2001 (A56); 92.9% to 20.2% for PMB2948 (B24); and 82.1% to 13.3% for PMB2707 (B44).

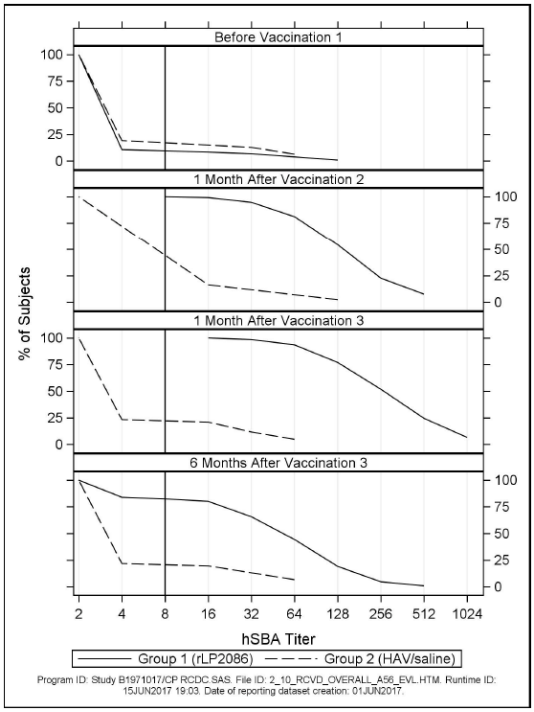
For Group 1 subjects aged ≥24 months to <4 years and aged ≥4 years to <10 years, from 1 month after the third vaccination to 6 months after the third vaccination, the proportion of subjects with an hSBA titre ≥1:16 decreased from 83.8% to 19.0% and 91.0% to 46.0%, respectively, for PMB80 (A22); 100.0% to 77.0% and 100.0% to 82.9%, respectively, for PMB2001 (A56); 81.0% to 9.2% and 88.9% to 20.3%, respectively, for PMB2948 (B24); and 80.0% to 9.1% and 75.4% 7.2%, respectively, for PMB2707 (B44).

For Group 1 subjects in the combined age stratum, from 1 month after the third vaccination to 6 months after the third vaccination, the proportion of subjects with an hSBA titre ≥1:16 decreased from 87.4% to 32.5% for PMB80 (A22); 100.0% to 80.2% for PMB2001 (A56); 84.9% to 14.7% for PMB2948 (B24); and 77.6% to 8.1% for PMB2707 (B44).

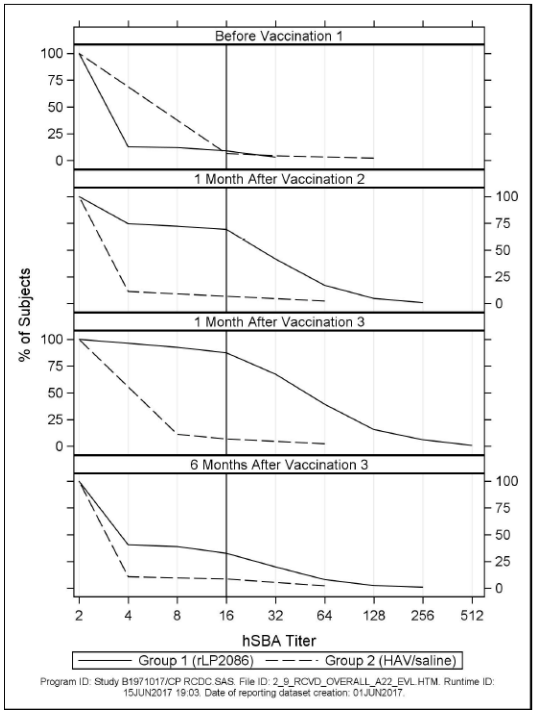
Reverse Cumulative Distribution Curves

The RCDCs of the proportions of subjects exhibiting an hSBA response (≥LLOQ) for each of the 4 primary strains and at each sampling time point, for the combined age stratum are provided in Figures below.

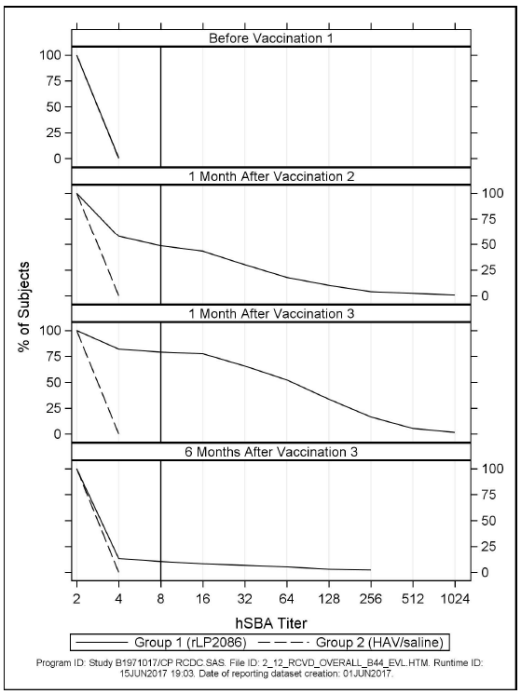
Reverse Cumulative Distribution Curves Age Strata: ≥24 Months to <10 Years – Evaluable Immunogenicity Population



PMB80 (A22)



PMB2001 (A56)



PMB2707 (B44)

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 12. Summary of Efficacy for trial B1971035

Title: A Phase 2, Randomized, Controlled, Observer-Blinded Study Conducted to Describe the Immunogenicity, Safety, and Tolerability of a Neisseria meningitidis Serogroup B Bivalent Recombinant Lipoprotein 2086 Vaccine (Bivalent rLP2086) when administered to Healthy Toddlers Aged 12 to <18 Months or 18 to <24 Months			
Study identifier	B1971035		
Design	A two stage randomized, HAV controlled, observer-blinded multicentre study.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 months not applicable not applicable
Hypothesis	Descriptive		
Treatments groups	Bivalent rLP2086		Bivalent rLP2086 at Month 0, 2 and 6. 294 subjects
	Paediatric HAV vaccine		paediatric HAV vaccine at Month 0 (Visit 1) and Month 6, saline at month 2. 106 subjects
Endpoints and definitions	Primary endpoints	% ≥LLOQ	% of subjects aged ≥12 months to <24 months with hSBA titre ≥LLOQ for each of the 4 primary MnB test strains 1 month after the third vaccination with bivalent rLP2086.
	Secondary endpoint	% ≥LLOQ	Proportion of subjects with hSBA titre ≥LLOQ for each of the 4 primary MnB test strains at other timepoints, namely 1 month after the second vaccination and 1 and 6 months after the third vaccination with bivalent rLP2086.
	Secondary endpoint	hSBA GMT	hSBA GMTs for each of the 4 primary test strains at baseline, 1 month after the second vaccination, and 1 and 6 months after the third vaccination with bivalent rLP2086

Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Evaluable immunogenicity population, 1 month after the third vaccination.				
Descriptive statistics and estimate variability	Treatment group		60µg rLP2086	120µg rLP2086	HAV/saline
	Number of subject		44	220	132
	Age group 12 to <24 months				
	% ≥ LLOQ per strain	A22	90.0%	89.6%	5.0%
			(68.3, 98.8)	(81.7, 94.9)	(1.0, 13.9)
		A56	100.0%	100.0%	1.9%
			(82.4, 100.0)	(96.2, 100.0)	(0.0, 9.9)
		B24	85.0%	71.6%	5.0%
			(62.1, 96.8)	(61.4, 80.4)	(1.0, 13.9)
		B44	89.5%	86.2%	0.0%
			(66.9, 98.7)	(77.5, 92.4)	(0.0, 6.6)

Notes	<free text>

Table 13. Summary of Efficacy for trial B1971017

Title: Phase 2, randomized, controlled, observer-blinded, multicentre study designed to assess the immunogenicity, safety, and tolerability of bivalent rLP2086 at the 120-µg dose level administered to healthy subjects aged ≥24 months to <10 years as part of a Month 0, 2, and 6 schedule.			
Study identifier	B1971017		
Design	A two stage randomized, HAV controlled, observer-blinded multicentre study.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 months not applicable not applicable	
Hypothesis	Descriptive		
Treatments groups	Bivalent rLP2086	Bivalent rLP2086 at Month 0, 2 and 6. 294 subjects	
	Paediatric HAV vaccine	paediatric HAV vaccine at Month 0 (Visit 1) and Month 6, saline at month 2. 106 subjects	
Endpoints and definitions	Primary endpoints	% ≥LLOQ	% of subjects aged ≥24 months to <4 years and proportion of subjects aged ≥4 years to <10 years with hSBA titre ≥LLOQ for each of the 4 primary MnB test strains 1 month after the third vaccination with bivalent rLP2086.
	Secondary endpoint	% ≥LLOQ	Proportion of subjects with hSBA titre ≥LLOQ for each of the 4 primary MnB test strains at 6 months after the third vaccination with bivalent rLP2086.

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Evaluable immunogenicity population, 1 month after the third vaccination.			
Descriptive statistics and estimate variability	Treatment group		rLP2086	HAV/saline
	Number of subject		274	97
	Age group 24 months – 4 years			
	% ≥ LLOQ per strain (1 m)	A22	83.8% (72.9, 91.6)	4.0% (0.1, 20.4)
		A56	100 % (94.7, 100.0)	4.2% (0.1, 21.1)
		B24	85.7% (74.6, 93.3)	7.7% (0.9, 25.1)
		B44	80.0% (68.2, 88.9)	0.0% (0.0, 13.2)
	Age group 4 years – 10 years			
	% ≥ LLOQ per strain (1 m)	A22	91.0% (81.5, 96.6)	10.0% (1.2, 31.7)
		A56	100 % (94.9, 100.0)	42.1% (20.3, 66.5)
		B24	(92.1) (82.4, 97.4)	0.0% (0.0, 16.8)
		B44	78.3% (66.7, 87.3)	0.0% (0.0, 14.2)

	Treatment group		rLP2086	HAV/saline
	Number of subject		274	97
	Age group 24 months – 4 years			
	% ≥ LLOQ per strain (6 m)	A22	19.0%	7.7%
			(10.2, 30.9)	(0.9, 25.1)
		A56	80.3%	16.7%
			(68.2, 89.4)	(4.7, 37.4)
		B24	9.2%	0.0%
			(3.5, 19.0)	(0.0, 13.2)
		B44	12.1%	0.0%
			(5.4, 22.1)	(0.0, 13.2)
	Age group 4 years – 10 years			
	% ≥ LLOQ per strain (6 m)	A22	46.0%	9.5%
			(33.4, 59.1)	(1.2, 30.4)
		A56	84.3%	22.7%
			(73.6, 91.9)	(7.8, 45.4)
		B24	21.9%	0.0%
			(12.5, 34.0)	(0.0, 16.1)
		B44	8.7%	0.0%
			(3.3, 18.0)	(0.0, 14.8)

Analysis performed across trials (pooled analyses and meta-analysis)

Response in children ≥1 – <10 years in relation to response in adolescents

The tables below provide the response to vaccination with 120 µg bivalent rLP2086 given as 0,2,6 m one month after the third dose in the different age strata as compared to children and adolescents aged ≥10 years to <18 years, in which bivalent rLP2086 is licensed . The response in those ≥10 years to <18 years is taken from the integrated summary of efficacy provided by the MAH.

Table 14. Proportion of subjects with hSBA >1:8 one month post third dose 120 µg bivalent rLP2086 given as 0,2,6 m

	≥12 months to < 24 months	≥24 months to < 4years	≥4 years to <10 years	≥10 years to <18 years
A22	n=96 89.6 (81.7, 94.9)	n=68 86.8 (76.4, 93.8)	n=67 98.5 (92.0, 100.0)	n=6033 94.9 (94.3, 95.5)
A56	n=95 100.0 (96.2, 100.0)	n=68 100.0 (94.7, 100.0)	n=71 100.0 (94.9, 100.0)	n=3547 99.3 (98.9, 99.5)
B24	n=95 71.6 (61.4, 80.4)	n=63 85.7 (74.6, 93.3)	n=63 92.1 (82.4, 97.4)	n=5944 90.1 (89.3, 90.8)
B44	n=94 86.2 (77.5, 92.4)	n=65 80.0 (68.2, 88.9)	n=69 78.3 (66.7, 87.3)	n=3513 86.1 (84.9, 87.2)

Table 15. GMTs 1 month post third dose 120 µg bivalent rLP2086 given as 0,2,6 m

	≥12 months to < 24 months	≥24 months to < 4years	≥4 years to <10 years	≥10 years to <18 years
A22	n=96 67.3 (53.7, 84.3)	n=68 33.7 (26.4, 42.9)	n=67 38.2 (30.6, 47.6)	n=6033 64.3 (62.8 - 65.9)
A56	n=95 171.4 (141.6, 207.4)	n=68 175.6 (139.1, 221.6)	n=71 191.0 (153.9, 237.1)	n=3547 159.0 (153.8 - 164.3)
B24	n=86 15.1 (12.3, 18.6)	n=63 19.1 (14.9, 24.5)	n=63 26.8 (21.3, 33.9)	n=5944 26.2 (25.5 - 26.9)
B44	n=94 45.6 (35.2, 59.0)	n=65 43.6 (29.9, 63.6)	n=69 36.5 (25.2, 52.7)	n=3513 37.1 (35.5 - 38.8)

Design and conduct of clinical studies

The MAH submitted two phase II in children aged 1 to 9 years which were agreed in the Paediatric Investigation Plan. Study B1971035 is a Phase 2, randomized, active-controlled, observer-blinded, multicentre study to assess the immunogenicity, safety, and tolerability of bivalent rLP2086 when administered as a 3-dose primary series to healthy children 12 to <24 months of age. B1971017 was a Phase 2, randomized, controlled, observer-blinded, multicentre study designed to assess the immunogenicity, safety, and tolerability of bivalent rLP2086 at the 120-µg dose level administered to healthy subjects aged ≥24 months to <10 years as part of a Month 0, 2, and 6 schedule. Both studies were descriptive in nature. Studies were adequately designed and well conducted.

2.4.2. Discussion on clinical efficacy

Efficacy data and additional analyses

Immunogenicity results from these Phase 2 studies of a 3-dose regimen (0-, 2-, and 6-month schedule) of 120 µg bivalent rLP2086 given to toddlers and children aged ≥12 months to <10 years are consistent with previous studies in adolescents and young adults.

Response in children ≥12 - <24 months

In children aged 12 to <24 months of age, of subjects achieving an hSBA titre ≥ LLOQ for each of the 4 primary MnB test strains 1 month after the third vaccination ranged from 85.0% to 100.0% for the 60-µg group and from 71.6% to 100.0% for the 120-µg group. Responses were similar for the two age groups (12-18 months and 18-24 months). These findings are further supported secondary endpoints including increases in GMTs.

The MAH concludes 3 doses of either 60 µg or 120 µg of bivalent rLP2086 administered on a 0-, 2-, 6-month schedule, induced robust immune responses in toddlers 12 to <24 months of age. This is agreed.

Half dose for children ≥12 - <24 months

Interestingly, although numbers were small, there was no marked benefit of the 120 µg dose compared to the 60µg dose. Conversely, for some timepoints, strains, and age strata there was a clear benefit of the 60 µg dose over the 120 µg dose. For example, the response against strain B24 one month after the second dose in children aged 12-18 months was 70% for the 60 µg compared to 24% for the 120 µg group. This was not seen in the older age strata (18-24 months), where the rates were 44% vs 43% respectively. Moreover, one month after the third dose there was no marked difference in response (% >LLOQ) or GMTs. Considering the small numbers, differences might be due to chance. However, as there

is no clear benefit of the 120 µg over the 60 µg the CHMP recommended the MAH to further explore the 60µg dose formulation in children <2 years. The MAH clarified that they have no further plans to evaluate the 60µg dose in children aged ≥12 to <24 months but are however planning to further evaluate this reduced dose in infants.

Response in children ≥24 months - <10 years

In children aged ≥24 months to <10 years, 1 month after the third dose of bivalent rLP2086 the proportion of subjects achieving an hSBA titre ≥LLOQ (1:8 for A56, B24 and B44; 1:16 for A22) for each of the 4 primary MnB test strains ranged from 80.0% to 100.0% for subjects aged ≥24 months to <4 years and from 78.3% to 100.0% for subjects ≥4 years to <10 years after 3 doses. These findings are further supported secondary endpoints including increases in GMTs.

Response in children ≥1 – <10 years in relation to response in adolescents

Considering the hSBA >1:8, which is slightly more conservative than the presumptive correlate for protection, there is no consistent effect of age on the response to vaccination. In children aged ≥12 months to <24 months the response varied from 71.6% to 100.0% dependent on strain, compared to 80.0% to 100.0% in children aged ≥24 months to <4 years, 78.3% to 100.0% in those ≥4 to <10 years and 86.1% to 99.3% in those aged ≥10 to <18 years of age. There is no clear and consistent effect of age for subjects ≥24 months of age. Broadly, the response one month after primary vaccination is similar in children aged ≥24 months to <10 years of age as compared to adolescents and is slightly lower in children aged ≥12 months to <24 months of age.

Persistence of response: durability of protection

The low hSBA titres 6 months after Vaccination 3 seen in study B1971017 suggest a steep decline in protection for strains A22, B24 and B44 following primary vaccination in children aged 2 to 10 years. The proportion of subjects achieving an hSBA titre ≥ LLOQ declined from a range of 87.4% , 88.9% and 79.1%1 month after Vaccination 3 to **32.5%, 15.5% and 10.4%** 6 months after Vaccination 3 for strains A22, B24 and B44 respectively. For strain A56 persistence was better, with the proportion of subjects achieving an hSBA titre ≥ LLOQ declining from 100% to 82.4% over the same period. There is no persistence data in younger children, aged ≥12 months to <2 years, and it can only be speculated that the persistence in these youngest age group will be worse.

These data show that a substantial proportion (70-90%) of vaccinated children aged ≥2 to <10 years could be unprotected within 6 months after completing their primary vaccination schedule against a majority of circulating MenB strains. As the decrease in antibody titres was larger in children aged ≥24 months to <4 years compared to those aged ≥4 years to 10 years, the proportion without protective antibody titres 6 months after primary vaccination is expected to be higher in the ≥12 to <24 month old age stratum. Therefore, based on the current data it was not possible to conclude on the vaccination in children between 1 and 9 years of age as the CHMP was concerned that the proposed vaccination schedule would not be adequate to ensure sufficient protection against *N. meningitidis* group B in children of this age group because the level of antibodies declined shortly after vaccination. An additional dose seemed to be required to ensure lasting protection, and more data were needed to support such use.

Results in adolescents (study B1971005) would suggest immune persistence being better in this older age group. In study B1971005, where the median age was 14 years, the proportion of subjects achieving an hSBA titre ≥ LLOQ declined from 95.3%, 100%, 93.3% and 95.7% one month after the third dose to 60.2%, 89.4%, 57.1% and 36.7% 6 months after the third dose for strains A22, A56, B24 and B44 respectively. A similar picture is seen in study B1971012/B1971033, where the mean age was 14.4 years, which showed better persistence still at 12 months after the third dose. No 6-month data were available for comparison. Potentially higher baseline titres in adolescents contribute to this improved persistence,

however there may simply be a better priming response in older children. In any case, a booster dose is recommended for adolescents for those who remain at risk of IMD.

There is no booster data available for children aged ≥ 1 to < 10 years of age. Post-booster response and persistence studies are 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. During the assessment of the Art 46 procedure (B1971017) it was concluded that persistence and booster data would be needed for the determination of an optimal dosing schedule in toddlers and young children. The MAH stated that they intend to submit the persistence and booster data from stage 2 of study B1971035 in the third quarter of 2020.

Considering that the posology as was proposed provided only limited benefit as it was of short duration for a majority of the strains tested against, the extension of the indication in children under 10 years of age was refused. However, the paediatric data related to these studies are included in the SmPC in agreement with the Paediatric Regulation. Therefore, the MAH was invited to submit an updated SmPC proposal which appropriately reflects the data from the paediatric studies in sections 4.8 and 5.1, as well as the statement regarding data in section 4.2 regarding the lack of data in subjects younger than 10 years, highlighting the limitations of the data.

2.4.3. Conclusions on the clinical efficacy

Based on an hSBA titre ≥ LLOQ for the 4 primary MnB test strains 1 month after Vaccination 3, children aged ≥12 months to 10 years had largely similar immune responses compared to adolescents (≥10 years to <19 years). A similar picture is seen with other immunogenicity endpoints, albeit based on GMTs the response in children aged ≥12 months to <24 months is slightly lower, also as compared to adolescents. It can be concluded that bivalent rLP2086 appears to be immunogenic in the ≥12 months to <10 years age population and is likely to offer protection against MnB infection similarly to that expected for adolescents based on the hSBA correlate of protection one month after the third dose. However, considering the rapid decay of antibodies seen in children aged 24 months and older, protection provided by the vaccine is expected to be significantly reduced during the first 6 months after primary vaccination. This means that protection conferred by the priming doses is insufficient to ensure durable protection, and expected benefit from this vaccine at the now proposed dosing regimen (0,2,6 m) is limited for children aged ≥12 months to <10 years and therefore a recommendation in this age group was refused. However, safety and efficacy findings from the clinical trials in children are being included in the SmPC in accordance with the paediatric regulation to especially reflect the persistence data and uncertainties around the persistence issue.

2.5. Clinical safety

Introduction

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 15,000 subjects who have been vaccinated with at least 1 dose of Trumenba in 11 completed clinical studies. 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.

The description of the safety of Trumenba in children aged 12 months to 9 years below is based on the summary of safety and integrated analysis of the two clinical studies (B1971017 and B1971035) in

support of this application. Further, the MAH refers to safety data collected in adolescents (including children aged 10 years and older) as a reference.

Patient exposure

The ***safety dataset for children*** comprises data derived from the 752 subjects who received 120 μg of bivalent rLP2086 or control in the 2 controlled studies (B1971035 and B1971017).

Subjects aged ≥12-<24 months: 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.

Subjects aged ≥24 months – 10 years: 294 subjects received 120 μg rLP2086 according to the 0,2,6 month schedule, 106 subjects received HAV/saline.

Adverse events

Local reactions

Subjects aged 12-<24 months

Overall, tenderness at the injection site was the most commonly reported local reaction for all vaccine groups and age strata. Redness at the injection site was the second most commonly reported local reaction followed by swelling at the injection site.

The median onset day for all types of local reactions ranged from 1 to 2 days for all groups. The median duration of tenderness at the injection site was 2 days (range of 1 to 9 days) for the 60-μg group, 2 days (range of 1 to 9 days) for the 120-μg group, and 1 day (range of 1 to 3 days) for the HAV/saline group after all 3 vaccinations. The median duration of redness was 2 days (range of 1 to 8 days) for the 60- μg group, 2 days (range of 1 to 11 days) for the 120- μg group, and 1 day (range of 1 to 8 days) for the HAV/saline group. The median duration of swelling was between 2 to 3 days (range of 1 to 9 days) for subjects in the 60- μg group, 1 day (range of 1 to 15 days) for the 120- μg group, and 1 day (range of 1 to 2 days) for the HAV/saline group.

Local reactions were two to three times more common in the 60 μg rLP2086 and 120 μg rLP2086 groups compared to the HAV/saline control group. Overall there is no difference in the incidence of local reactions between the 60 μg and 120 μg group, however there is a trend for more severe local reactions in the 120 μg group after all doses. The proportion of subjects reporting potentiation for any local reaction was 0.0% to 4.5% and 0.0% to 2.8% for subjects in the 60-μg and 120-μg groups, respectively.

Table 16. Subjects Reporting Local Reactions by Maximum Severity Within 7 Days After Vaccination – 12 to <24 Months – Safety Population (Clinical Study Report, Protocol B1971035)

	Vaccine Group (as Administered)											
	60 μg rLP2086				**120 μg rLP2086**				**HAV/Saline**			
	N	**n**	**(%)**	**(95% CI)**	**N**	**n**	**(%)**	**(95% CI)**	**N**	**n**	**(%)**	**(95% CI)**
First dose												
Tenderness at injection site a												
Any	44	26	(59.1)	(43.2, 73.7)	220	127	(57.7)	(50.9, 64.3)	132	23	(17.4)	(11.4, 25.0)
Mild	44	16	(36.4)	(22.4, 52.2)	220	68	(30.9)	(24.9, 37.5)	132	21	(15.9)	(10.1, 23.3)
Moderate	44	9	(20.5)	(9.8, 35.3)	220	50	(22.7)	(17.4, 28.8)	132	2	(1.5)	(0.2, 5.4)
Severe	44	1	(2.3)	(0.1, 12.0)	220	9	(4.1)	(1.9, 7.6)	132	0	(0.0)	(0.0, 2.8)
Redness b												
Any	44	24	(54.5)	(38.8, 69.6)	220	103	(46.8)	(40.1, 53.6)	132	20	(15.2)	(9.5, 22.4)
Mild	44	15	(34.1)	(20.5, 49.9)	220	63	(28.6)	(22.8, 35.1)	132	20	(15.2)	(9.5, 22.4)
Moderate	44	9	(20.5)	(9.8, 35.3)	220	37	(16.8)	(12.1, 22.4)	132	0	(0.0)	(0.0, 2.8)
Severe	44	0	(0.0)	(0.0, 8.0)	220	3	(1.4)	(0.3, 3.9)	132	0	(0.0)	(0.0, 2.8)

Swelling b												
Any	44	13	(29.5)	(16.8, 45.2)	220	63	(28.6)	(22.8, 35.1)	132	13	(9.8)	(5.3, 16.3)
Mild	44	8	(18.2)	(8.2, 32.7)	220	38	(17.3)	(12.5, 22.9)	132	13	(9.8)	(5.3, 16.3)
Moderate	44	5	(11.4)	(3.8, 24.6)	220	24	(10.9)	(7.1, 15.8)	132	0	(0.0)	(0.0, 2.8)
Severe	44	0	(0.0)	(0.0, 8.0)	220	1	(0.5)	(0.0, 2.5)	132	0	(0.0)	(0.0, 2.8)
Any local reaction c												
	44	32	(72.7)	(57.2, 85.0)	220	157	(71.4)	(64.9, 77.2)	132	34	(25.8)	(18.5, 34.1)
Second dose												
Tenderness at injection site a												
Any	44	21	(47.7)	(32.5, 63.3)	212	113	(53.3)	(46.3, 60.2)	128	19	(14.8)	(9.2, 22.2)
Mild	44	16	(36.4)	(22.4, 52.2)	212	68	(32.1)	(25.8, 38.8)	128	18	(14.1)	(8.6, 21.3)
Moderate	44	5	(11.4)	(3.8, 24.6)	212	39	(18.4)	(13.4, 24.3)	128	1	(0.8)	(0.0, 4.3)
Severe	44	0	(0.0)	(0.0, 8.0)	212	6	(2.8)	(1.0, 6.1)	128	0	(0.0)	(0.0, 2.8)
Redness b												
Any	44	18	(40.9)	(26.3, 56.8)	212	76	(35.8)	(29.4, 42.7)	128	10	(7.8)	(3.8, 13.9)
Mild	44	15	(34.1)	(20.5, 49.9)	212	48	(22.6)	(17.2, 28.9)	128	10	(7.8)	(3.8, 13.9)
Moderate	44	3	(6.8)	(1.4, 18.7)	212	28	(13.2)	(9.0, 18.5)	128	0	(0.0)	(0.0, 2.8)
Severe	44	0	(0.0)	(0.0, 8.0)	212	0	(0.0)	(0.0, 1.7)	128	0	(0.0)	(0.0, 2.8)
Swelling b												
Any	44	10	(22.7)	(11.5, 37.8)	212	43	(20.3)	(15.1, 26.3)	128	6	(4.7)	(1.7, 9.9)
Mild	44	7	(15.9)	(6.6, 30.1)	212	29	(13.7)	(9.4, 19.1)	128	6	(4.7)	(1.7, 9.9)
Moderate	44	3	(6.8)	(1.4, 18.7)	212	13	(6.1)	(3.3, 10.3)	128	0	(0.0)	(0.0, 2.8)
Severe	44	0	(0.0)	(0.0, 8.0)	212	1	(0.5)	(0.0, 2.6)	128	0	(0.0)	(0.0, 2.8)
Any local reaction c												
	44	29	(65.9)	(50.1, 79.5)	212	131	(61.8)	(54.9, 68.4)	128	27	(21.1)	(14.4, 29.2)
Third dose												
Tenderness at injection site a												
Any	44	25	(56.8)	(41.0, 71.7)	212	121	(57.1)	(50.1, 63.8)	128	20	(15.6)	(9.8, 23.1)
Mild	44	14	(31.8)	(18.6, 47.6)	212	68	(32.1)	(25.8, 38.8)	128	16	(12.5)	(7.3, 19.5)
Moderate	44	11	(25.0)	(13.2, 40.3)	212	42	(19.8)	(14.7, 25.8)	128	4	(3.1)	(0.9, 7.8)
Severe	44	0	(0.0)	(0.0, 8.0)	212	11	(5.2)	(2.6, 9.1)	128	0	(0.0)	(0.0, 2.8)
Redness b												
Any	44	17	(38.6)	(24.4, 54.5)	212	70	(33.0)	(26.7, 39.8)	128	10	(7.8)	(3.8, 13.9)
Mild	44	13	(29.5)	(16.8, 45.2)	212	44	(20.8)	(15.5, 26.8)	128	9	(7.0)	(3.3, 12.9)
Moderate	44	4	(9.1)	(2.5, 21.7)	212	25	(11.8)	(7.8, 16.9)	128	1	(0.8)	(0.0, 4.3)
Severe	44	0	(0.0)	(0.0, 8.0)	212	1	(0.5)	(0.0, 2.6)	128	0	(0.0)	(0.0, 2.8)
Swelling b												
Any	44	10	(22.7)	(11.5, 37.8)	212	48	(22.6)	(17.2, 28.9)	128	7	(5.5)	(2.2, 10.9)
Mild	44	5	(11.4)	(3.8, 24.6)	212	29	(13.7)	(9.4, 19.1)	128	6	(4.7)	(1.7, 9.9)
Moderate	44	5	(11.4)	(3.8, 24.6)	212	18	(8.5)	(5.1, 13.1)	128	1	(0.8)	(0.0, 4.3)
Severe	44	0	(0.0)	(0.0, 8.0)	212	1	(0.5)	(0.0, 2.6)	128	0	(0.0)	(0.0, 2.8)
Any local reaction c												
	44	28	(63.6)	(47.8, 77.6)	212	131	(61.8)	(54.9, 68.4)	128	24	(18.8)	(12.4, 26.6)
After any dose												
Tenderness at injection site a												
Any	44	35	(79.5)	(64.7, 90.2)	220	160	(72.7)	(66.3, 78.5)	132	41	(31.1)	(23.3, 39.7)
Mild	44	17	(38.6)	(24.4, 54.5)	220	67	(30.5)	(24.4, 37.0)	132	36	(27.3)	(19.9, 35.7)
Moderate	44	17	(38.6)	(24.4, 54.5)	220	74	(33.6)	(27.4, 40.3)	132	5	(3.8)	(1.2, 8.6)
Severe	44	1	(2.3)	(0.1, 12.0)	220	19	(8.6)	(5.3, 13.2)	132	0	(0.0)	(0.0, 2.8)
Redness b												
Any	44	30	(68.2)	(52.4, 81.4)	220	137	(62.3)	(55.5, 68.7)	132	28	(21.2)	(14.6, 29.2)
Mild	44	19	(43.2)	(28.3, 59.0)	220	75	(34.1)	(27.9, 40.8)	132	27	(20.5)	(13.9, 28.3)
Moderate	44	11	(25.0)	(13.2, 40.3)	220	58	(26.4)	(20.7, 32.7)	132	1	(0.8)	(0.0, 4.1)
Severe	44	0	(0.0)	(0.0, 8.0)	220	4	(1.8)	(0.5, 4.6)	132	0	(0.0)	(0.0, 2.8)
Swelling b												
Any	44	17	(38.6)	(24.4, 54.5)	220	103	(46.8)	(40.1, 53.6)	132	20	(15.2)	(9.5, 22.4)
Mild	44	8	(18.2)	(8.2, 32.7)	220	54	(24.5)	(19.0, 30.8)	132	19	(14.4)	(8.9, 21.6)
Moderate	44	9	(20.5)	(9.8, 35.3)	220	46	(20.9)	(15.7, 26.9)	132	1	(0.8)	(0.0, 4.1)
Severe	44	0	(0.0)	(0.0, 8.0)	220	3	(1.4)	(0.3, 3.9)	132	0	(0.0)	(0.0, 2.8)
Any local reaction c												
	44	38	(86.4)	(72.6, 94.8)	220	181	(82.3)	(76.6, 87.1)	132	52	(39.4)	(31.0, 48.3)

N = number of subjects with known values after the vaccination. n = Number of subjects reporting maximum severity of mild, moderate, or severe based on the severity scales. Exact 2-sided CI based upon observed proportion of subjects, using the Clopper and Pearson method.

a. Mild = hurts if gently touched, moderate = hurts if gently touched with crying, severe = causes limitation of limb movement.

b. Mild is 0.5 to 2.0 cm (1 to 4 caliper units), moderate is 2.5 to 7.0 cm (5 to 14 caliper units), and severe is >7.0 cm (>14 caliper units).

c. Any local reaction = any tenderness at injection site, any redness, or any swelling.

Subjects aged ≥24 months to <10 years

For the combined age stratum, the bivalent rLP2086 group reported more local reactions than those subjects receiving HAV/saline. Among bivalent rLP2086 recipients, pain at the injection site (84.4%) was the most commonly reported local reaction followed by redness (60.2%) and swelling (46.6%) after any vaccination, compared to 33.0%, 17.0% and 9.4% in the HAV/saline group, respectively.

Table 17. Injection site reactions in study B1971017

	bivalent rLP2086	HAV/saline group
Pain at the injection site	84.4%	33.0%
Redness	60.2%	17.0%
Swelling	46.6%	9.4%

These differences were similar after each vaccination, regardless of whether the subjects in the comparator group received the HAV vaccine (Vaccination 1 and 3) or saline (Vaccination 2).

The proportion of subjects reporting pain at the injection site was higher in subjects aged ≥4 years to <10 years (92.6%) when compared to subjects ≥24 months to <4 years (75.9%).

Most local reactions were mild or moderate in severity, with ≤7.1% of bivalent rLP2086 recipients reporting severe local reactions after any vaccination (compared to 0.0% for HAV/saline recipients). The median onset of local reactions after any vaccination was 1 to 2 days after bivalent rLP2086 vaccination and lasted a median of 1 to 2 days. The proportion of subjects in both groups with severity increase with potentiation for pain at the injection site, redness, and swelling was low, and generally similar between subjects in both age strata. After any bivalent rLP2086 vaccination, older children reported more injection site pain (92.6%) than their younger counterparts (75.9%).

Among the combined age stratum, severe local reactions (>14 caliper units) occurred during the study at low rates after any bivalent rLP2086 vaccination. There was 1 subject who received HAV/saline and was withdrawn from the study because of local reactions (injection site hypersensitivity and injection site pruritus).

Systemic Reactions

Subjects aged 12-<24 months

The incidence of systemic events by maximum severity within 7 days after each vaccination and any vaccination by investigational product is presented for the combined age stratum (12 to <24 months) in Table 16.

Systemic reactions were more commonly reported in the rLP2086 groups compared to the HAV/saline group. There is no clear difference in the rate of systemic reactions between the 60- µg and 120- µg group. After the first dose a slightly higher rate in the 120- µg group (75.9% as compared to 70.5% for the 60- µg group) reported any systemic reaction, however considering any dose there is no difference (85.0% vs 86.4%). Also considering the severity of systemic reactions, there is no clear trend of increased severity with the higher dose group.

The rate of systemic adverse events was lower in children 18 months or older compared to those <18 months of age. For subjects 12 to <18 months of age, systemic events after any vaccination were reported by 95.5% and 89.1% of subjects in the 60-µg and 120-µg groups, respectively compared to 66.7% of subjects in the HAV/saline group. For subjects 18 to <24 months of age, systemic events after any vaccination were reported by 77.3% and 80.9% of subjects in the 60-µg and 120-µg groups, respectively compared to 59.1% of subjects in the HAV/saline group.

Fever

For the combined age stratum (12 to <24 months), fever (≥38°C) after any vaccination was reported by 36.4% and 37.3% of subjects in the 60- µg and 120- µg groups, respectively compared to 15.2% of subjects in the HAV/saline group. The rate of fever in the rLP2086 groups decreased with each dose.

For subjects 12 to <18 months of age, fever (≥38°C) after any vaccination was reported by 40.9% and 38.2% of subjects in the 60- µg and 120- µg groups, respectively, compared to 31.8% and 36.4% of subjects 18 to <24 months of age.

Overall one subject (0.5%) in the 120- µg group reported fever >40.0°C.

Table 18. Subjects Reporting Systemic Event by Maximum Severity Within 7 Days After Vaccination – 12 to <24 Months –Safety Population

	60 µg rLP2086				120 µg rLP2086				HAV/Saline			
	N	n	(%)	(95% CI)	N	n	(%)	(95% CI)	N	n	(%)	(95% CI)
First dose												
Fever												
≥38°C	44	16	(36.4)	(22.4, 52.2)	220	61	(27.7)	(21.9, 34.1)	132	8	(6.1)	(2.7, 11.6)
38.0° to <38.5°C	44	9	(20.5)	(9.8, 35.3)	220	16	(7.3)	(4.2, 11.5)	132	5	(3.8)	(1.2, 8.6)
38.5° to <39.0°C	44	5	(11.4)	(3.8, 24.6)	220	31	(14.1)	(9.8, 19.4)	132	1	(0.8)	(0.0, 4.1)
39.0° to <39.5°C	44	0	(0.0)	(0.0, 8.0)	220	9	(4.1)	(1.9, 7.6)	132	2	(1.5)	(0.2, 5.4)
39.5° to ≤40.0°C	44	2	(4.5)	(0.6, 15.5)	220	4	(1.8)	(0.5, 4.6)	132	0	(0.0)	(0.0, 2.8)
>40.0°C	44	0	(0.0)	(0.0, 8.0)	220	1	(0.5)	(0.0, 2.5)	132	0	(0.0)	(0.0, 2.8)
Irritability d												
Any	44	25	(56.8)	(41.0, 71.7)	220	146	(66.4)	(59.7, 72.6)	132	49	(37.1)	(28.9, 46.0)
Mild	44	8	(18.2)	(8.2, 32.7)	220	39	(17.7)	(12.9, 23.4)	132	16	(12.1)	(7.1, 18.9)
Moderate	44	16	(36.4)	(22.4, 52.2)	220	94	(42.7)	(36.1, 49.6)	132	31	(23.5)	(16.5, 31.6)
Severe	44	1	(2.3)	(0.1, 12.0)	220	13	(5.9)	(3.2, 9.9)	132	2	(1.5)	(0.2, 5.4)
Drowsiness e												
Any	44	19	(43.2)	(28.3, 59.0)	220	97	(44.1)	(37.4, 50.9)	132	24	(18.2)	(12.0, 25.8)
Mild	44	15	(34.1)	(20.5, 49.9)	220	58	(26.4)	(20.7, 32.7)	132	15	(11.4)	(6.5, 18.0)
Moderate	44	4	(9.1)	(2.5, 21.7)	220	30	(13.6)	(9.4, 18.9)	132	8	(6.1)	(2.7, 11.6)
Severe	44	0	(0.0)	(0.0, 8.0)	220	9	(4.1)	(1.9, 7.6)	132	1	(0.8)	(0.0, 4.1)
Loss of or decreased appetite f												
Any	44	16	(36.4)	(22.4, 52.2)	220	100	(45.5)	(38.7, 52.3)	132	30	(22.7)	(15.9, 30.8)
Mild	44	9	(20.5)	(9.8, 35.3)	220	45	(20.5)	(15.3, 26.4)	132	14	(10.6)	(5.9, 17.2)
Moderate	44	5	(11.4)	(3.8, 24.6)	220	44	(20.0)	(14.9, 25.9)	132	13	(9.8)	(5.3, 16.3)
Severe	44	2	(4.5)	(0.6, 15.5)	220	11	(5.0)	(2.5, 8.8)	132	3	(2.3)	(0.5, 6.5)
Use of antipyretic medication												
	44	23	(52.3)	(36.7, 67.5)	220	103	(46.8)	(40.1, 53.6)	132	26	(19.7)	(13.3, 27.5)
Any systemic event g												
	44	31	(70.5)	(54.8, 83.2)	220	167	(75.9)	(69.7, 81.4)	132	60	(45.5)	(36.8, 54.3)
Second dose												

Fever												
≥38°C	44	5	(11.4)	(3.8, 24.6)	212	30	(14.2)	(9.8, 19.6)	128	6	(4.7)	(1.7, 9.9)
38.0° to <38.5°C	44	3	(6.8)	(1.4, 18.7)	212	14	(6.6)	(3.7, 10.8)	128	5	(3.9)	(1.3, 8.9)
38.5° to <39.0°C	44	1	(2.3)	(0.1, 12.0)	212	10	(4.7)	(2.3, 8.5)	128	1	(0.8)	(0.0, 4.3)
39.0° to <39.5°C	44	0	(0.0)	(0.0, 8.0)	212	4	(1.9)	(0.5, 4.8)	128	0	(0.0)	(0.0, 2.8)
39.5° to ≤40.0°C	44	1	(2.3)	(0.1, 12.0)	212	2	(0.9)	(0.1, 3.4)	128	0	(0.0)	(0.0, 2.8)
>40.0°C	44	0	(0.0)	(0.0, 8.0)	212	0	(0.0)	(0.0, 1.7)	128	0	(0.0)	(0.0, 2.8)
Irritability d												
Any	44	20	(45.5)	(30.4, 61.2)	212	116	(54.7)	(47.8, 61.5)	128	32	(25.0)	(17.8, 33.4)
Mild	44	13	(29.5)	(16.8, 45.2)	212	40	(18.9)	(13.8, 24.8)	128	9	(7.0)	(3.3, 12.9)
Moderate	44	6	(13.6)	(5.2, 27.4)	212	70	(33.0)	(26.7, 39.8)	128	20	(15.6)	(9.8, 23.1)
Severe	44	1	(2.3)	(0.1, 12.0)	212	6	(2.8)	(1.0, 6.1)	128	3	(2.3)	(0.5, 6.7)
Drowsiness e												
Any	44	7	(15.9)	(6.6, 30.1)	212	65	(30.7)	(24.5, 37.3)	128	15	(11.7)	(6.7, 18.6)
Mild	44	6	(13.6)	(5.2, 27.4)	212	39	(18.4)	(13.4, 24.3)	128	9	(7.0)	(3.3, 12.9)
Moderate	44	1	(2.3)	(0.1, 12.0)	212	23	(10.8)	(7.0, 15.8)	128	5	(3.9)	(1.3, 8.9)
Severe	44	0	(0.0)	(0.0, 8.0)	212	3	(1.4)	(0.3, 4.1)	128	1	(0.8)	(0.0, 4.3)
Loss of or decreased appetite f												
Any	44	11	(25.0)	(13.2, 40.3)	212	77	(36.3)	(29.8, 43.2)	128	23	(18.0)	(11.7, 25.7)
Mild	44	10	(22.7)	(11.5, 37.8)	212	41	(19.3)	(14.3, 25.3)	128	12	(9.4)	(4.9, 15.8)
Moderate	44	1	(2.3)	(0.1, 12.0)	212	26	(12.3)	(8.2, 17.5)	128	10	(7.8)	(3.8, 13.9)
Severe	44	0	(0.0)	(0.0, 8.0)	212	10	(4.7)	(2.3, 8.5)	128	1	(0.8)	(0.0, 4.3)
Use of antipyretic medication												
	44	16	(36.4)	(22.4, 52.2)	212	71	(33.5)	(27.2, 40.3)	128	19	(14.8)	(9.2, 22.2)
Any systemic event g												
	44	27	(61.4)	(45.5, 75.6)	212	130	(61.3)	(54.4, 67.9)	128	43	(33.6)	(25.5, 42.5)
Third dose												
Fever												
≥38°C	44	2	(4.5)	(0.6, 15.5)	212	27	(12.7)	(8.6, 18.0)	128	8	(6.3)	(2.7, 11.9)
38.0° to <38.5°C	44	2	(4.5)	(0.6, 15.5)	212	14	(6.6)	(3.7, 10.8)	128	5	(3.9)	(1.3, 8.9)
38.5° to <39.0°C	44	0	(0.0)	(0.0, 8.0)	212	5	(2.4)	(0.8, 5.4)	128	2	(1.6)	(0.2, 5.5)
39.0° to <39.5°C	44	0	(0.0)	(0.0, 8.0)	212	5	(2.4)	(0.8, 5.4)	128	1	(0.8)	(0.0, 4.3)
39.5° to ≤40.0°C	44	0	(0.0)	(0.0, 8.0)	212	3	(1.4)	(0.3, 4.1)	128	0	(0.0)	(0.0, 2.8)
>40.0°C	44	0	(0.0)	(0.0, 8.0)	212	0	(0.0)	(0.0, 1.7)	128	0	(0.0)	(0.0, 2.8)
Irritability d												
Any	44	16	(36.4)	(22.4, 52.2)	212	107	(50.5)	(43.5, 57.4)	128	35	(27.3)	(19.8, 35.9)
Mild	44	9	(20.5)	(9.8, 35.3)	212	50	(23.6)	(18.0, 29.9)	128	16	(12.5)	(7.3, 19.5)

Moderate	44	7	(15.9)	(6.6, 30.1)	212	53	(25.0)	(19.3, 31.4)	128	17	(13.3)	(7.9, 20.4)
Severe	44	0	(0.0)	(0.0, 8.0)	212	4	(1.9)	(0.5, 4.8)	128	2	(1.6)	(0.2, 5.5)
Drowsiness e												
Any	44	6	(13.6)	(5.2, 27.4)	212	72	(34.0)	(27.6, 40.8)	128	17	(13.3)	(7.9, 20.4)
Mild	44	6	(13.6)	(5.2, 27.4)	212	50	(23.6)	(18.0, 29.9)	128	13	(10.2)	(5.5, 16.7)
Moderate	44	0	(0.0)	(0.0, 8.0)	212	18	(8.5)	(5.1, 13.1)	128	3	(2.3)	(0.5, 6.7)
Severe	44	0	(0.0)	(0.0, 8.0)	212	4	(1.9)	(0.5, 4.8)	128	1	(0.8)	(0.0, 4.3)
Loss of or decreased appetite f												
Any	44	8	(18.2)	(8.2, 32.7)	212	73	(34.4)	(28.1, 41.2)	128	23	(18.0)	(11.7, 25.7)
Mild	44	7	(15.9)	(6.6, 30.1)	212	36	(17.0)	(12.2, 22.7)	128	16	(12.5)	(7.3, 19.5)
Moderate	44	0	(0.0)	(0.0, 8.0)	212	31	(14.6)	(10.2, 20.1)	128	6	(4.7)	(1.7, 9.9)
Severe	44	1	(2.3)	(0.1, 12.0)	212	6	(2.8)	(1.0, 6.1)	128	1	(0.8)	(0.0, 4.3)
Use of antipyretic medication												
	44	8	(18.2)	(8.2, 32.7)	212	72	(34.0)	(27.6, 40.8)	128	19	(14.8)	(9.2, 22.2)
Any systemic event g												
	44	19	(43.2)	(28.3, 59.0)	212	134	(63.2)	(56.3, 69.7)	128	49	(38.3)	(29.8, 47.3)
After any dose												
Any Fever												
≥38°C	44	16	(36.4)	(22.4, 52.2)	220	82	(37.3)	(30.9, 44.0)	132	20	(15.2)	(9.5, 22.4)
38.0° to <38.5°C	44	8	(18.2)	(8.2, 32.7)	220	22	(10.0)	(6.4, 14.7)	132	13	(9.8)	(5.3, 16.3)
38.5° to <39.0°C	44	5	(11.4)	(3.8, 24.6)	220	34	(15.5)	(10.9, 20.9)	132	4	(3.0)	(0.8, 7.6)
39.0° to <39.5°C	44	0	(0.0)	(0.0, 8.0)	220	16	(7.3)	(4.2, 11.5)	132	3	(2.3)	(0.5, 6.5)
39.5° to ≤40.0°C	44	3	(6.8)	(1.4, 18.7)	220	9	(4.1)	(1.9, 7.6)	132	0	(0.0)	(0.0, 2.8)
>40.0°C	44	0	(0.0)	(0.0, 8.0)	220	1	(0.5)	(0.0, 2.5)	132	0	(0.0)	(0.0, 2.8)
Irritability d												
Any	44	31	(70.5)	(54.8, 83.2)	220	176	(80.0)	(74.1, 85.1)	132	69	(52.3)	(43.4, 61.0)
Mild	44	9	(20.5)	(9.8, 35.3)	220	40	(18.2)	(13.3, 23.9)	132	21	(15.9)	(10.1, 23.3)
Moderate	44	20	(45.5)	(30.4, 61.2)	220	116	(52.7)	(45.9, 59.5)	132	42	(31.8)	(24.0, 40.5)
Severe	44	2	(4.5)	(0.6, 15.5)	220	20	(9.1)	(5.6, 13.7)	132	6	(4.5)	(1.7, 9.6)
Drowsiness e												
Any	44	23	(52.3)	(36.7, 67.5)	220	127	(57.7)	(50.9, 64.3)	132	40	(30.3)	(22.6, 38.9)
Mild	44	19	(43.2)	(28.3, 59.0)	220	70	(31.8)	(25.7, 38.4)	132	23	(17.4)	(11.4, 25.0)
Moderate	44	4	(9.1)	(2.5, 21.7)	220	42	(19.1)	(14.1, 24.9)	132	14	(10.6)	(5.9, 17.2)
Severe	44	0	(0.0)	(0.0, 8.0)	220	15	(6.8)	(3.9, 11.0)	132	3	(2.3)	(0.5, 6.5)
Loss of or decreased appetite f												
Any	44	22	(50.0)	(34.6, 65.4)	220	142	(64.5)	(57.8, 70.9)	132	50	(37.9)	(29.6, 46.7)
Mild	44	13	(29.5)	(16.8, 45.2)	220	51	(23.2)	(17.8, 29.3)	132	25	(18.9)	(12.6, 26.7)

Moderate	44	6	(13.6)	(5.2, 27.4)	220	68	(30.9)	(24.9, 37.5)	132	21	(15.9)	(10.1, 23.3)
Severe	44	3	(6.8)	(1.4, 18.7)	220	23	(10.5)	(6.7, 15.3)	132	4	(3.0)	(0.8, 7.6)
Use of antipyretic medication												
	44	25	(56.8)	(41.0, 71.7)	220	134	(60.9)	(54.1, 67.4)	132	45	(34.1)	(26.1, 42.8)
Any systemic event g												
	44	38	(86.4)	(72.6, 94.8)	220	187	(85.0)	(79.6, 89.4)	132	83	(62.9)	(54.0, 71.1)

d. Mild = easily consolable, moderate = requiring increased attention, severe = inconsolable; crying cannot be comforted.
e. Mild = increased or prolonged sleeping bouts, moderate = slightly subdued interfering with daily activity, severe = disabling not interested in usual daily activity.
f. Mild = decreased interest in eating, moderate = decreased oral intake, severe = refusal to feed.
g. Any systemic event does not include consideration of the use of antipyretic medication.

Subjects ≥24 months to <10 years

For the combined age stratum, the bivalent rLP2086 group reported higher rates of systemic reactogenicity events after any vaccination than subjects receiving HAV/saline. Headache (33.3%) and fatigue (59.5%) were the most commonly reported systemic events among recipients of any bivalent rLP2086 dose.

There were substantial differences for fever (24.5% vs 12.3%, respectively), headache (33.3% vs 20.8%, respectively), fatigue (59.5% vs 38.7%, respectively), muscle pain (28.2% vs 8.5%, respectively), joint pain (14.6% vs 6.6%, respectively), and antipyretic use (51.0% vs 28.3%, respectively) (see table).

Table 19. Systemic reactions in study B1971017

	bivalent rLP2086	HAV/saline group
Fever	24.5%	12.3%
Headache	33.3%	20.8%
Fatigue	59.5%	38.7%
muscle pain	28.2%	8.5%
joint pain	14.6%	6.6%
antipyretic use	51.0%	28.3%

Only fever and headache appeared to have differences by age stratum with fever more common in the younger age stratum and headache more common in the older age stratum. Fever was more common in the children aged ≥24 months to <4 years than children aged ≥4 years to <10 years for both bivalent rLP2086 and HAV/saline recipients (30.3% vs 18.8% and 18.2% vs 5.9%, respectively). Headache was more common in the children aged ≥4 years to <10 years than children aged ≥24 months to <4 years for both bivalent rLP2086 and HAV/saline recipients (45.6% vs 20.7% and 35.3% vs 7.3%, respectively). The younger bivalent rLP2086 stratum was more likely to experience vomiting, diarrhea and fatigue than the older age stratum.

Most cases of fever were <39°C, with 6.1% of subjects receiving bivalent rLP2086 and 4.7% of subjects receiving HAV/saline reporting fever 38.0°C to <38.5°C, and 6.1% for bivalent rLP2086 1 and 1.9% for HAV/saline reporting fever 38.5°C to <39.0°C. Fever >40°C was reported for 1 (0.3%) subject who received bivalent rLP2086 but was not reported for any of the subjects receiving HAV/saline.

Systemic events in the bivalent rLP2086 group were generally mild or moderate in severity, and severe systemic events were infrequent (0 to 6.5% after any vaccination). The median onset of systemic events after each vaccination was 1 to 3 days after bivalent rLP2086 vaccination and lasted a median of 1 to 4 days. The severity (potentiation) of systemic reactogenicity did not increase with subsequent dosing for subjects aged ≥4 years to <10 years. Of subjects aged ≥24 months to <4 years, 3.7% reported any severity increases with potentiation.

No subject withdrew from the study because of a systemic event.

Other AEs

Subjects aged 12-<24 months

(Non-related) AEs reported by subjects in both age strata and all vaccine groups were consistent with those health conditions and illnesses typically observed in the respective age groups in the general population, including were upper respiratory tract infection, irritability, bronchitis, gastroenteritis and pharyngitis.

Related AEs

For subjects 12 to <18 months of age, a total of 0 (0.0%) subjects in the 60-µg group, 13 (11.8%) subjects in the 120-µg group, and 3 (4.5%) subjects in the HAV/saline group reported related AEs. Related AEs reported in the *120-µg group* were pyrexia (5 subjects [4.5%]), diarrhoea (4 subjects [3.6%]), irritability (4 subjects [3.6%]), injection site pain (3 subjects [2.7%]), somnolence (2 subjects [1.8%]), and chills (2 subjects [1.8%]) and single events of vomiting, postvaccinal irritability, vaccination site pain, and decreased appetite. Related AEs reported in the *HAV/saline group* were 2 events of decreased appetite (1 subject [1.5%]), 2 events of somnolence (1 subject [1.5%]) and single events of diarrhoea, postvaccinal irritability, and vaccination site erythema.

For subjects 18 to <24 months of age, a total of 6 (27.3%) subjects in the 60-µg group, 10 (9.1%) subjects in the 120-µg group, and 3 (4.5%) subjects in the HAV/saline group reported related AEs. Related AEs reported in the *60-µg group* were irritability (3 subjects [13.6%]) and single events of injection site erythema, injection site pain, pyrexia, vaccination site pain, and decreased appetite. Related AEs reported in the *120-µg group* were pyrexia (3 subjects [2.7%]) rash (2 subjects [1.8%]), 2 events of irritability (1 subject [0.9%]), and single events of vomiting, chills, injection site bruising, injection site nodule, injection site pain, and erythema. Related AEs reported in the *HAV/saline group* were irritability (2 subjects [3.0%]) and single events of crying and vaccination site pain.

Subjects ≥24 months to <10 years

For the combined age stratum, the percentages of subjects with AEs occurring within 30 days of each vaccination or after any vaccination were similar between bivalent rLP2086 and HAV/saline recipients, with overall rates during the vaccination phase of 62.6% and 63.2%, respectively. The rate of AEs assessed as related by the investigators was 2.4% vs 0.0% for the bivalent rLP2086 and HAV/saline groups in younger children and 2.4% vs 1.9%, respectively in the older age strata. Most AEs were mild or moderate in severity and the frequency and severity of AEs did not increase with subsequent vaccinations.

For subjects in the bivalent rLP2086 group, AEs were primarily from the SOC of infections and infestations (86 of the 90 subjects reporting AEs in the younger age stratum, and 85 of the 94 subjects reporting AEs in the older age stratum), with respiratory infections being the most frequent AEs reported. Two (2) subjects in the bivalent rLP2086 group withdrew from the study because of AEs, both of which were considered related to investigational product by the investigator.

Serious adverse event/deaths/other significant events

Other Significant Events

Subjects aged 12-<24 months

The proportion of subjects reporting at least 1 MAE within 30 days after any vaccination was 31.8%, 36.4%, and 35.6% for subjects in the 60-µg, 120-µg, and HAV/saline groups, respectively. The

proportion of subjects reporting at least 1 MAE during the vaccination phase was 40.9%, 50.9%, and 43.2% for subjects in the 60-µg, 120-µg, and HAV/saline groups, respectively.

For the combined age stratum during the vaccination phase, MAEs deemed related to investigational product by investigators were reported by 0.0%, 2.3%, and 0.0% of subjects in the 60-µg, 120-µg, and HAV/saline groups, respectively.

Subjects ≥24 months to <10 years

Overall, for the combined age stratum, the proportion of subjects with at least 1 Medically Attended Event (MAE) occurring throughout the study was 48.6% for the bivalent rLP2086 group and 50.0% for the HAV/saline group. Among subjects reporting at least 1 MAE within 30 days after each vaccination or after any vaccination during the study, there were only minor differences between those receiving bivalent rLP2086 and HAV/saline, and no clinically meaningful differences in the proportion of subjects reporting MAEs after each subsequent vaccination.

During the vaccination phase, the proportions of subjects reporting MAEs were no different between children aged ≥24 months to <4 years and children aged ≥4 years to <10 years, and were similar between those receiving bivalent rLP2086 and HAV/saline (45.5% vs 40.9% and 41.8% vs 51.0%, respectively). This was consistent for MAEs reported throughout the study. Most events were mild or moderate after bivalent rLP2086 vaccination.

Serious adverse events & Deaths

Subjects aged 12-<24 months

For the combined age stratum, there was 1 (2.3%) subject in the 60-µg group, 8 (3.6%) subjects in the 120-µg group, and 4 (3.0%) subjects in the HAV/saline group reporting at least 1 SAE within 30 days after any vaccination. Throughout the entire AE collection period, 4 (9.1%) subjects in the 60-µg group, 19 (8.6%) subjects in the 120-µg group, and 8 (6.1%) subjects in the HAV/saline group reported at least 1 SAE. None of the SAEs were considered related to vaccine by the investigator what is agreed.

SAEs during the vaccination phase are presented in the table.

There were no deaths.

Subjects ≥24 months to <10 years

The proportion of subjects in the combined age stratum reporting at least 1 SAE within 30 days of any vaccination was similar between bivalent rLP2086 recipients and HAV/saline recipients, 1.0% compared to 0.9%, respectively. Throughout the study, 5 SAEs (1.7%) were reported in the bivalent rLP2086 group, 4 during the vaccination phase and 1 during follow-up. One (1) of the SAEs was considered related by the investigator - a case of transient hip synovitis in a 2-year-old male subject with onset on Day 1 after Vaccination 2.

One (1) immediate AE was reported during the study - severe injection site pain following Vaccination 3 with bivalent rLP2086. The injection site pain resolved and did not lead to discontinuation from the study. Autoimmune and neuroinflammatory conditions (as defined by a comprehensive list of MedDRA preferred terms), deaths, and NDCMCs were not reported in either the bivalent rLP2086 or HAV/saline recipients at any time during the study.

Among subjects from both age strata, those receiving bivalent rLP2086 were more likely to report days of missed school because of an AE than the HAV/saline group (23.1% vs 15.1%, respectively). Considering days of missed school because of related AEs the rates were 0.3% vs 0.0%, respectively. When school was missed, the median number of days missed was 4.5 days versus 4.0 days, respectively. One (1) subject in the bivalent rLP2086 group reported missing school (2 days) because of a related AE.

No subjects died during the study.

Discontinuation due to adverse events

In children who received 120 µg of bivalent rLP2086, four subjects (0.8%) discontinued due to an adverse event.

Two (1.8%) subjects, both 12 to <18 months of age and in the 120-µg group, were withdrawn for safety-related reasons during the study period covered in this report. One subject was withdrawn because of an SAE of unrelated, transient (<1 day) eyelid ptosis. The other subject was withdrawn because of related decreased appetite, injection site pain, irritability, and somnolence.

In children aged 24 months – 10 years, 2 [1.4%] subjects in the bivalent rLP2086 group in the 24 month to <4 year age stratum were withdrawn for safety-related reasons for reported AEs that led to discontinuation. Both subjects reported synovitis (see above).

Post marketing experience

Summary of Post-Marketing Data From the Safety Database: Patients Younger Than 10 Years of Age

The safety database was searched to identify PM adverse events for patients younger than 10 years of age receiving bivalent rLP2086. The estimated cumulative worldwide unit distribution for bivalent rLP2086 from US launch through 23 May 2018 is approximately 2,199,301 doses. Cumulatively a total of 1645 cases received from spontaneous sources through the cutoff date of 23 May 2018. Of the cases providing patient age, 44 involved children younger than 10. The majority (39) contained terms consistent with off-label use or medication errors but not clinical adverse events. One of the 5 reports reporting associated clinical adverse events was serious.

Detailed case level characteristics are summarized in Table 20.

Table 20. Cases From Spontaneous Sources Through 23 May 2018- Patients Younger Than 10 Years of Age

Characteristics	**Details**	**No. of Cases**
Country Where Event Occurred	United States	37
	Germany	3
	Portugal	2
	Cyprus	1
	Greece	1
Case Seriousness	Serious	1
	Non serious	43
Age Range (Years, n = 42)	28 days to 23 months	30

Characteristics	Details	No. of Cases
Min = 0.08 Years Max = 9 Years Mean = 2.2 Median = 0.88	2 to 9 years	14
Sex	Female	14
	Male	13
	Unknown	17
Case Outcome	Resolved	1
	Resolving	2
	Unknown	41
Patient History	Present	4
	Unknown/Not provided	40
Co-Suspect Medications (including vaccines)	None	40
	Present	4
Concomitant Medications (including vaccines)	None/Not provided	2
	Present	11
	Unknown/Not provided	31

For the cumulative period, a total of 83 AEs terms were reported for the 44 patients younger than 10 years of age. Table 21 summarizes the number of event terms by MedDRA SOC.

Table 21. Adverse Event Term by MedDRA SOC Involving Patients Younger Than 10 Years of Age

MedDRA SOC	Number of Events
Injury, poisoning and procedural complications	56
General disorders and administration site conditions	12
Psychiatric disorders	3
Blood and lymphatic system disorders	3
Cardiac disorders	1
Investigations	4
Metabolism and nutrition disorders	2

Table 21. Adverse Event Term by MedDRA SOC Involving Patients Younger Than 10 Years of Age

MedDRA SOC	Number of Events
Infections and infestations	1
Nervous system disorders	1

The most commonly reported adverse events (≥2.0%), irrespective of SOCs, are summarized in Table 22.

Table 22. Adverse Event Terms With Frequency ≥2% Involving Patients Younger Than 10 Years of Age

MedDRA PT	Number of Events	AE Reporting Proportion[a]
Drug administered to patient of inappropriate age	28	63.6%
Wrong drug administered	17	38.6%
Pyrexia	5	11.4%
Drug prescribing error	4	9.1%
Inappropriate schedule of drug administration	4	9.1%
Fatigue	2	4.5%
Incomplete course of vaccination	2	4.5%
Irritability	2	4.5%

a. AE reporting proportion (%) is calculated by dividing the number of AEs by the total number of spontaneous cases involving patients younger than 10 years (44).

Cases with No Associated Adverse Events

Of the total 44 PM cases involving patients younger than 10 years, the majority of patients (39) did not experience any clinical adverse events. These cases can be grouped in 2 subgroups:

1. Off-label use

There were 16 cases reporting off-label use (vaccine administered to patient of inappropriate age) of bivalent rLP2086 with no adverse events associated. these cases originated from the US (11), Germany (3), Greece, and Portugal (1 each). Of the 16 cases, 9 were infants (ranging from 10 weeks and 18 months of age); in 1 case a specific age was not provided.

2. Medication error

There were 23 cases reporting 4 unique PTs indicative of medication errors; more than 1 medication error PT was reported in some cases. There were 17 infants (between 1 and 18 months of age) and other 6 children (aged between 2 and 9 years).

Cases Reporting Non-Serious Adverse Events

There were 4 cases (1 off-label and 3 medication error cases) involving patients who developed fever following bivalent rLP2086 administration:

- One case, from Cyprus, involved an 8-year old female patient who was intentionally administered by the physician (off-label use) with bivalent rLP2086 and developed Pyrexia (39°C), Malaise, Asthenia, and Fatigue an unspecified number of days after the vaccination. At the time of the report the patient was recovering.
- One case, from the US, involved a 12-month-old female patient who received bivalent rLP2086 instead of the 4th dose of 13-valent pneumococcal conjugated vaccine (13vPnC), along with MMR vaccine, and varicella zoster vaccine. She developed, on the same day, low grade fever and fatigue, from which she recovered.
- One case, from the US, of a 12-month-old female patient who received bivalent rLP2086 instead of the intended vaccine, along with *Haemophilus influenzae* type b vaccine, Hepatitis A vaccine, MMR vaccine, and varicella zoster vaccine. On the same day she developed high fever (value not provided), and sleep disturbance which began 5 hours after being given bivalent rLP2086.
- One case, from the US, of a 5-month-old male patient who received bivalent rLP2086 instead of 13vPnC along with Hepatitis B vaccine, rotavirus vaccine, and ergocalciferol. The following day, the patient had low grade fever (value not specified), vaccination site pain, and irritability. The outcome of the adverse event was unknown at the time of the report.

Case Reporting Serious Adverse Events

A serious case from the US of a 1-month-old female patient who was supposed to receive the second dose of Hepatitis B vaccine and was instead inadvertently given bivalent rLP2086 (Medication error). The following day she was admitted to the hospital with high fever (39.6 C), poor feeding, elevated liver enzymes, neutropenia, anaemia, thrombocytopenia, and hypertonia. The cerebrospinal fluid revealed no growth after 48 hours. There was no growth from blood or urine cultures either. The final diagnosis was aseptic meningitis secondary to inflammatory response due to the erroneous administration of the meningococcal B vaccine. Ampicillin, ceftazidime, and acyclovir were empirically started at the admission, then discontinued. The patient started recovering and was discharged from the hospital 4 days later. A product quality and manufacturing review was unremarkable for batch specification deviations.

2.5.1. Discussion on clinical safety

Bivalent rLP2086 was well tolerated by children aged ≥12 months to <10 years. The data show that bivalent rLP2086 is a reactogenic vaccine, with a relatively high proportion of subjects reporting local and systemic reactions. Only one subject (n=1, 0.2%) discontinued the vaccine due to reactogenicity however; the majority of events were mild to moderate and transient with only very limited number of cases with potentiation.

Reactions in children aged 12 to <24 months and 24 months to <10 years

Among 120 µg bivalent rLP2086 recipients aged 12 to <24 months, tenderness at the injection site (72.7%) was the most commonly reported local reaction followed by redness (62.3%) and swelling (46.8%) after any vaccination. The most frequently reported local reaction for children aged 24 months to <10 years was pain at the injection site, 84.4%. This was lower as compared to adolescents receiving bivalent rLP2086 in Study B1971009, 92.6%. As highlighted by the MAH, this could be related to the ability of older individuals to better report pain, resulting in a reporting bias. Redness were more prominent among the children aged 12 to <24 months and 2 to <10 years than among the adolescents in

Study B1971009, 62.3% and 60.2% vs 24.1%, respectively. Swelling was reported by 46.8% and 46.6% vs 27.4%, respectively.

For children aged 12 to < 24 months, irritability (80.0%), loss of or decreased appetite (64.5%) and drowsiness (57.7%) were the most common systemic reactions. Considering the rates of systemic reactions in subjects aged 2 to 10 years as compared to subjects aged 10- to 25-years (Study B1971009 and Study B1971016), headache (33.3% vs 33% to 52%, respectively) and fatigue (59.5% vs 36% to 54%, respectively) were the most common systemic events reported for bivalent rLP2086 recipients, and use of antipyretics to self-treat symptoms during the 7 days following vaccination was 51% vs 12% to 21%, respectively. Antipyretic use in children aged 12 to < 24 months was 60.9%.

Fever (≥38.0°C) was more common in children aged 12 to < 24 months (37.3%) and children aged 24 months to <10 years (24.5%) compared to 1.2% to 6% for bivalent rLP2086 recipients aged 10 years to 25 years. Fever was also more common under young children aged 24 months to <4 years, of whom 30.3% reported fever (≥38.0°C) after any vaccination, compared to children aged ≥4 years to <10 years, where 18.8% reported fever (≥38.0°C) after any vaccination. Of note, 11.4% of subjects aged 12 to < 24 months and 9.7% of subjects aged ≥24months to <4 years reported fever ≥39.0°C, this was 3.3% for children aged ≥4 to <10 years. 0.5% of children 12 to <24 months and 1.4% of children 24months to <4 years reported fever >40°C, whilst no children aged ≥4 to <10 years reported fever >40°C. The majority of fevers were low grade and normalized within 2 days after vaccination. Fever rates declined with subsequent vaccinations. There were no febrile seizures reported. As approximately 10% of children under 4 will experience a high fever ≥39.0°C following vaccination, which is considered significant, this should be mentioned explicitly in the product information.

60µg vs 120µg in children aged 12 to <24 months

There is no clear difference in the safety profile with the 60µg dose as compared to the 120 µg dose apart from severe local reactions (tenderness, redness and swelling), which – albeit rare – appear to be more common following the full dose.

Other AEs

The percentages of bivalent rLP2086 recipients reporting AEs and MAEs within 30 days after any vaccination were similar to those reported for control recipients. Severe events were rare, as were related events. The percentage of subjects reporting AEs was higher (58.2% in children aged 1 to <2 years, 44.2% in children aged 2 to <10 years) than that reported among the 13,275 bivalent rLP2086 recipients in 8 previously reported studies (30.6%). The majority of AEs were infections and infestations common for children aged 1 to <10 years. This is within expectation.

The percentages of children aged 1 to <10 years experiencing SAEs was similar in those who received 120 µg of bivalent rLP2086 on a 0-, 2-, and 6-month schedule vs those who received control vaccine within 30 days after any dose (2.1% vs 2.1%). This was 0.6% vs 0.7% in adolescents, respectively.

Hip synovitis

In children, 1 (0.2%) subject who received 120 µg of bivalent rLP2086 was reported with a related SAE - a case of transient hip synovitis in a 2-year-old male subject who received bivalent rLP2086. The synovitis began 1 day following Vaccination 2, did not require hospitalization, and resolved after 13 days without sequelae after the child received anti-inflammatory therapy. The subject was withdrawn from the study and did not receive the third dose.

The 2 additional non serious cases of synovitis also occurred in subjects receiving bivalent rLP2086. One (1) case of related hip synovitis was diagnosed in a 3-year-old male subject 3 days after Vaccination 2 and spontaneously resolved 3 days after the onset of the event without any intervention. The subject was withdrawn by the investigator and did not receive the third dose. The subject also had recovered from a

viral upper respiratory infection 10 days prior to onset of the synovitis. The third case of synovitis was unrelated knee synovitis occurring in a 6-year-old female 16 days after Vaccination 2 and 24 days after recovery from a viral upper respiratory infection. It resolved after 5 days with ibuprofen treatment and the subject continued participation in the study, receiving Vaccination 3 without incident or recurrence.

Transient hip synovitis is a usually benign self-limiting condition. Reported annual incidences around 0.2% and 76.2 per 100,000 person-years in a general population, these would be higher in children aged 2-10 years as the mean age of onset is 6 years [Asche et al Chiropractic & Manual therapies 2013, 21:39]. If the indication were to be extended to include children this age, special attention should be given to the occurrence of transient hip synovitis following bivalent rLP2086. The MAH is requested to provide in the next PSUR a cumulative review the occurrence of transient hip synovitis and related AEs in relation to bivalent rLP2086. This cumulative review should include all type of sinovitis and also arthritis and reactive arthritis.

Additional expert consultations

Advice Vaccines Working Party (VWP)

The VWP unanimously agreed that in this case there is a combination of factors that requires data on duration of protection and response to booster doses to be available pre-approval. Therefore, it was recommended to wait until data from study 35 (ongoing) become available. If this study shows that children of 1-2 years of age mount an anamnestic response following a booster at 12 months after the third dose, it might be possible to approve use with a booster from 1-9 years even though the booster should probably be given between 6-12 months and not at 12 months.

2.5.2. Conclusions on clinical safety

Trumenba is a reactogenic vaccine, with higher rates of reactions seen in younger children up to the age of 10 as compared to adolescents. Approximately 10% of children aged 1 to <4 years will develop fever ≥39.0°C following vaccination, which is considered significant and should be mentioned specifically in the SmPC. This information is updated in the SmPC.

In addition, the MAH should submit the following safety data within the next PSUR: *a cumulative review the occurrence of transient hip synovitis and related AEs in relation to bivalent rLP2086. This cumulative review should include all type of sinovitis and also arthritis and reactive arthritis. . If relevant a thorough discussion on the need for any updates of the ongoing routine signal evaluation activities (e.g. AE follow-up forms), RMP or product information should be included.*

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application. The variation proposes to lower the approved indication for Trumenba to include 1-9 year olds. The MAH submitted an updated RMP version (v2.0) with this application.

The *main proposed RMP changes* were the following:

- Product overview: Indication and posology updated to reflect the proposed extension of use in individuals from 1 year old.
- Addition in Module SIII on clinical trial exposure to include exposure data for children between 1 and 9 years.
- Update of Module SIV on populations not studied in clinical trials to reflect the proposed infant variation.
- The updated version is presented in the new EU-RMP format (as per Revision 2 of GVP Module V).

The MAH has decided to change the scope of the current variation to update the Trumenba SmPC, and not to change the indication. Therefore, the RMP version 2 is not reflecting anymore the authorised indication and cannot be considered approvable; RMP version 3.0 remains as the latest approved. The Rapporteurs' proposed changes to the list of safety concerns are further assessed in another ongoing procedure (EMEA/H/C/004051/II/0023).

The PRAC considered that the risk management plan version 2.0 is not acceptable. RMP version 3.0 (as approved in the later variation II/0023) remains as the latest approved.

2.7. Update of the Product information

As a result of this variation, sections 4.2, 4.8 and 5.1 of the SmPC are being updated to include relevant data in children aged 1 to 10 years and inform the use in this age group. The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 3 which includes all agreed changes to the Product Information.

2.7.1. User consultation

N/A

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Trumenba (bivalent rLP2086) is a bivalent lipoprotein 2086 vaccine that consists of two purified recombinant lipoprotein 2086 (rLP2086) antigens, from each of the factor H binding protein (fHBP) subfamilies (A and B, A05 and B01). Bivalent rLP2086 is intended for active immunisation *to prevent invasive meningococcal disease caused by Neisseria meningitidis serogroup B.* It is currently licensed to be used in children aged 10 years or older, adolescents and adults. With the current procedure the MAH intends to extend the use to children aged 1 to <10 years.

3.1.2. Available therapies and unmet medical need

Since the introduction of conjugated Meningococcal C vaccines in Europe, *Neisseria meningitidis* serogroup B (MnB) has been a leading cause of invasive meningococcal disease (IMD). Risk factors for the development of meningococcal disease include age (<5 years of age with a second peak in adolescents and young adults), deficiencies in the terminal complement pathway, functional or anatomic asplenia and underlying chronic disease.

In 2016 there were 3280 notified cases of MnB invasive disease in Europe. The notification rate in children under the age of 1 was 8.49 per 100.000, compared to 2.67 in children aged 1 to 4 years, 0.61 per 100.000 in children aged 5 to 14 years and 1.07 per 100.000 in adolescents and young adults aged 15 to 24 years. While the incidence of endemic disease has decreased in all age groups and is currently at a relatively low level globally, the rapid progression to serious illness or death, potentially life-changing long-term morbidities associated with IMD, and the shortcomings of mass chemoprophylaxis, emphasize the need for availability of safe and effective MnB vaccines to reduce the impact of MnB disease.

In 2013 Bexsero, a MnB vaccine based on four different MnB antigens: NHBA, NadA, fHbp, and PorA P1.4, was approved in Europe for the prevention of MnB disease in individuals 2 months of age and older.

3.1.3. Main clinical studies

This application is supported by 2 clinical studies: B1971035 and B1971017

As it is not feasible to demonstrate protective efficacy of MnB vaccines, the licensure is based on a serological marker, serum bactericidal antibody. Serum bactericidal antibody assays measure functional antibody activity in human sera that results in the complement-dependent killing of the target meningococcal strains. An hSBA titre ≥ 1:4 is a presumptive correlate for protection for MnB. Throughout the studies the lower limit of quantitation (LLOQ) corresponded with an hSBA titre ≥ 1:8 or higher, dependent on strain. Therefore, this measure is relatively conservative.

B1971035 is a phase 2 randomised active (HAV/saline) controlled observer blinded multicentre study in 396 children 12 to <24 months of age. This study contains two stages: stage 1, which evaluates the primary vaccination and stage 2, which assesses the duration of the immune response and the response to a booster dose. The first stage of the study was designed to assess the immunogenicity, safety, and tolerability of bivalent rLP2086 when administered as a 3-dose primary series at Months 0, 2, and 6. It included a sentinel phase in which a sentinel enrolment phase in which a half dose of the vaccine (60 µg) was given to children aged 12 to <15 months and 18 to <24 months of age, 44 in total, before moving to a full dose of the vaccine (120 µg) in the same age cohorts. Only data from stage 1 are contained within the current submission. The MAH intends to submit the persistence and booster data from stage 2 of this study in the third quarter of 2020.

B1971017 is a Phase 2, randomized (3:1), HAV/saline controlled, observer-blinded study to describe the immunogenicity, safety, and tolerability of bivalent rLP2086 in 400 healthy subjects aged ≥24 months to <4 years and ≥4 years to <10 years.

In addition, the MAH submitted an extrapolation exercise from children and adolescents aged 10 to 18 years to children aged 1 to 9 years.

3.2. Favourable effects

Subjects aged ≥12 to <24 months

Of subjects aged 12 to <24 months, one month after the third dose of 120 µg of bivalent rLP2086, 89.6%, 100.0%, 71.6% and 86.2% had a hSBA titre ≥ LLOQ against primary test strains A22, A56, B24 and B44, respectively. In subjects aged 12 to <24 months who received 60 µg of bivalent rLP2086, 90.0%, 100.0%, 85.0% and 89.5% had a hSBA titre ≥ LLOQ against primary test strains A22, A56, B24 and B44, respectively.

The rates of hSBA titre ≥ LLOQ were largely similar to what was previously observed in adolescents (≥10 years to <19 years), for whom bivalent rLP2086 is authorised, albeit based on GMTs the response in children aged ≥12 months to <24 months is slightly lower compared to adolescents.

Subjects aged ≥24 months to <10 years

The proportion of subjects aged ≥24 months to <4 years and ≥4 years to <10 years with an hSBA titre ≥ LLOQ at 1 month after the third vaccination with bivalent rLP2086 given at 0,2,6 m was 83.8% and 91.0%, respectively, for A22; 100.0% for both age strata for A56; 85.7% and 92.1%, respectively, for B24; and 80.0% and 78.3%, respectively, for B44. The rate of hSBA titre ≥ LLOQ was largely similar to what was previously observed in adolescents (≥10 years to <19 years).

For subjects aged ≥24 months to <4 years 6 months after the third vaccination the proportion of subjects with an hSBA titre ≥LLOQ decreased to 19.0% for A22; 80.3% for A56; 9.2% for B24; and 12.1% for B44. For subjects aged ≥4 years to <10 years 6 months after the third vaccination the proportion of subjects with an hSBA titre ≥ LLOQ had decreased to 46.0% for A22; 84.3% for A56; 21.9% for B24; and 8.7% for B44.

3.3. Uncertainties and limitations about favourable effects

In children aged ≥12 months to <24 months, only few subjects have been exposed to the half dose. As a result, confidence intervals around point estimates are wide. No inferential testing between the half, 60µg dose, and the full, 120 µg, dose was planned for.

There is no hSBA persistence data for children aged ≥12 to <24 months. For children aged ≥24 months to <10 years, there is persistence of hSBA measured at 6 months post third dose however data between 1 month after the third dose and 6 months after the third dose were not collected so the decay curve is unknown.

There is no booster data available for children aged ≥12 months to <10 years. Without booster response data in the young children, aged ≥12 months to <24 months, we do not know whether priming was adequate.

The age-related decline in persistence is not predicted by the antibody response as measured 1-month post dose 3. It is unclear which factors of the immune response are responsible for this faster decline in antibodies with younger age. Therefore, there is too much uncertainty to extrapolate the immunogenicity conclusions from children and adolescents aged 11-18 years to younger children (aged 1-9 years).

3.4. Unfavourable effects

Subjects aged ≥12 to <24 months

Among 120 µg bivalent rLP2086 recipients, tenderness at the injection site (72.7%) was the most commonly reported local reaction followed by redness (62.3%), and swelling (46.8%) after any vaccination, compared to 31.1%, 21.2%, and 15.2% in the HAV/saline group, respectively.

Subjects in the 120 µg bivalent rLP2086 and HAV/saline groups reported the following systemic reactions: fever (≥38°C) (37.3% and 15.2%, respectively), irritability (80.0% and 52.3%, respectively), drowsiness (57.7% and 30.3%, respectively), loss of or decreased appetite (64.5% and 37.9%, respectively), and antipyretic medication use (60.9% and 34.1%, respectively).

One subject discontinued from the study because of related decreased appetite, injection site pain, irritability, and somnolence.

There were no SAEs which were considered related to bivalent rLP2086.

Subjects aged ≥24 months to <10 years

Pain at the injection site (84.4%) was the most commonly reported local reaction followed by redness (60.2%) and swelling (46.6%) after any vaccination, compared to 33.0%, 17.0% and 9.4% in the HAV/saline group, respectively.

The bivalent rLP2086 group reported higher rates of systemic reactogenicity events after any vaccination than subjects receiving HAV/saline. These differences were substantial for fever (24.5% vs 12.3%, respectively), headache (33.3% vs 20.8%, respectively), fatigue (59.5% vs 38.7%, respectively), muscle pain (28.2% vs 8.5%, respectively), and joint pain (14.6% vs 6.6%, respectively). Antipyretic use in the bivalent group vs HAV/saline group was 51.0% vs 28.3%.

One SAE was considered related to bivalent rLP2086 by the investigator - a case of transient hip synovitis in a 2-year-old male subject with onset 1 day after Vaccination 2. Two subjects in the bivalent rLP2086 group withdrew from the study because of the AE of synovitis, both of which were considered related to investigational product by the investigator.

3.5. Uncertainties and limitations about unfavourable effects

The safety database in children aged ≥12 months to <24 months and ≥24 months to 10 years is relatively limited: 514 (120 µg bivalent rLP2086), 44 (60 µg bivalent rLP2086). This includes 294 subjects aged ≥24 months to <10 years and 220 subjects aged ≥12 months to <24 months exposed to 120 µg bivalent rLP2086. It is insufficient in size to exclude the occurrence of serious but rare adverse reactions.

3.6. Effects Table

Table 23. Effects Table for Trumenba in children aged ≥12 months to <10 years

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Children aged ≥12 to <24 months						
hSBA ≥ LLOQ	Response 1 month after 3rd dose (0,2,6) against primary strains (A22, A56, B24, B44)					
A22		%	89.6	5.0	(81.7, 94.9)	CSR B1971035
A56		%	100.0	1.9	(96.2, 100.0)	
B24		%	71.6	5.0	(61.4, 80.4)	
B44		%	86.2	0.0	(77.5, 92.4)	

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Children aged ≥24 months to <10 years						
hSBA ≥ LLOQ	Response 1 month after 3rd dose (0,2,6) against primary strains (A22, A56, B24, B44)					
A22		%	87.4	6.7	(80.6, 92.5)	
A56		%	100.0	20.9	(97.4, 100.0)	
B24		%	88.9	4.3	(82.1, 93.8)	
B44		%	79.1	0.0	(71.2, 85.6)	
Children aged ≥24 months to <10 years						
hSBA ≥ LLOQ	Response 6 months after 3rd dose (0,2,6) against primary strains (A22, A56, B24, B44)					
A22		%	32.5	8.5	(24.5, 41.5)	
A56		%	82.4	19.6	(74.8, 88.5)	
B24		%	15.5	0.0	(9.7, 22.9)	
B44		%	10.4	0.0	(5.8, 16.8)	
Unfavourable Effects						
Children aged ≥12 to <24 months						
Fever	≥38°C	%	37.3	15.2	(30.9, 44.0)	Table 23, CSR B1971035
	≥39°C	%	11.8	2.3	-	
Children aged ≥24 months to <4 years						
Fever	≥38°C	%	30.3	18.2	(23.0, 38.5)	Table 26, CSR B1971017
	≥39°C	%	9.7	1.8	-	
Children aged ≥4 years to <10 years						
Fever	≥38°C	%	18.8	5.9	(6.7, 18.0)	Table 27, CSR B1971017
	≥39°C	%	3.4	0.0	-	

Abbreviations: hSBA=human Serum Bactericidal Assay, LLOQ=Lower Limit of Quantification
Notes: Only favourable and unfavourable effects for the 120µg dose given at 0,2,6 months are presented

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Within the main clinical studies, a functional immune response has been demonstrated against four primary strains which have been selected from a MnB SBA strain pool of invasive disease isolates collected in Europe and the US. The MnB strain pool from which test strains were selected is similar in make-up and distribution of fHBP variants compared to contemporary, recently (2011-2014) collected MnB strains from the UK, the Netherlands, Canada and the US, therefore results of the main clinical trials can be considered relevant to the current situation.

Responses following three doses given at 0,2 and 6 months were relatively strong against all the strains tested against. One month after the third dose of 120µg bivalent rLP2086, 71.6-100.0% of subjects aged ≥12 to <24 months had an hSBA titre ≥ LLOQ for the 4 primary MnB test strains.

For subjects aged ≥24 months to <4 years this was 80.0 - 100.0%, and for subjects aged ≥4 years to <10 years this was 78.3-100.0%.

Broadly, the response one month after primary vaccination is similar in children aged ≥24 months to <10 years of age as compared to adolescents and is slightly lower in children aged ≥12 months to <24 months of age.

Bivalent rLP2086 is a fairly reactogenic vaccine with a high proportion of subjects reporting local and systemic reactions. Approximately 10% of children aged 1 to 4 years developed high fever (≥39°C) following vaccination with bivalent rLP2986. This is considered significant.

The persistence data in children aged ≥24 months to <10 years show that persistence is poor for the A22, B24 and B44 strain. After 6 months the proportion of subjects with an hSBA titre ≥ LLOQ had decreased to 32.5% for A22, 15.5% for B24 and 10.4% for B44. The decline was sharper in younger children, <4 years, as compared to the children ≥4 years of age. Although hSBA levels remained high against the A56 strain (declined from 100% to 82.4%), the data show that the priming doses are insufficient to ensure durable protection. A primary series of vaccination at 0,2,6 m provides only limited benefit as it is of short duration for a majority of the strains tested against for in children aged 2 to 10 years.

Results in adolescents (studies B1971005, B1971012/B1971033) would suggest immune persistence being better in this older age group. Potentially higher baseline titres in adolescents contribute to this improved persistence, however there may simply be a better priming response in older children. In any case, a booster dose is recommended for adolescents for those who remain at risk of IMD.

It was concluded that, with the available data at the moment, the proposed vaccination schedule was inadequate to ensure durable protection for the requested indication (≥1 to <10 years). An additional dose seems required and data to support such a recommendation are needed.

It is noted that the MAH is planning an additional Phase 3 clinical study of bivalent rLP2086 in children 1 to 9 years of age. The MAH is recommended to include the evaluation of a booster dose earlier than 2 years post primary vaccination in the target group; considering the waning antibody titres observed it would seem sensible to recommend a fourth dose 6 months post primary.

The response in children aged ≥12 to <24 months was similar following the 60µg dose given at 0,2 and 6 months as compared to the 120 µg dose, albeit based on very limited data, pointing towards no clear benefit of the whole dose over the half dose in this age group.

As data with the half dose are very limited and as the study was not designed for inferential testing, conclusions made based on this data are only preliminary and further confirmation would be needed. Moreover, there is no marked difference in the reactogenicity profile of the 60µg dose compared to the 120µg dose. Fever rates were similar between the two doses, as were the rates for most reactions measured. There is some indication however that there might be more severe local reactions with the higher dose, although these are rare. The MAH clarified that they have no further plans to evaluate the 60µg dose in children aged ≥12 to <24 months but are however planning to further evaluate this reduced dose in infants.

3.7.2. Balance of benefits and risks

The overall B/R of Trumenba remains unchanged for children aged 10 years and older for the currently proposed vaccination schedule.

3.8. Conclusions

The overall B/R of Trumenba is positive for children aged from 10 years of age for the currently proposed vaccination schedule.

An extension of indication of Trumenba in children from 1 to 9 years is not approvable at the moment with the current data. An update to SmPC 4.2, 4.4, 4.8, 5.1 to update efficacy and safety data related to studies B1971017 and B1971035 were agreed.

The overall B/R of Trumenba is positive.

In addition, the applicant should submit the following safety data with the next PSUR:

The MAH is requested to provide in the next PSUR a cumulative review the occurrence of transient hip synovitis and related AEs in relation to bivalent rLP2086. This cumulative review should include all type of sinovitis and also arthritis and reactive arthritis. If relevant a thorough discussion on the need for any updates of the ongoing routine signal evaluation activities (e.g. AE follow-up forms), RMP or product information should be included.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC based on the results from two paediatric studies: B1971017 and B1971035. The MAH took the opportunity to carry out typographical and linguistic improvements throughout the PI. The Package Leaflet is updated in accordance. The RMP version 2.0 has also been submitted.

In addition, the Marketing authorisation holder (MAH) took the opportunity to submit a corrected version of the final report of study B1971016, which was included in the initial marketing authorisation application.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II, IIIA and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0013/2017 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion Trumenba-H-C-4051-II-13