14 December 2017
EMA/CHMP/752098/2017
Human Medicines Evaluation Division

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

Trumenba

Meningococcal group B vaccine (recombinant, adsorbed)

Procedure no: EMEA/H/C/004051/P46/009

Note

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

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1. Introduction

On 1 September 2017, the MAH submitted a completed paediatric study for Trumenba, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

No changes to the SmPC are proposed.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study B1971017, 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 is a standalone study. The study was part of the paediatric investigation plan (PIP).

2.2. Information on the pharmaceutical formulation used in the study

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

• Study B1971017, 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.

2.3.2. Clinical study

Study B1971017

Description

B1971017 was a Phase 2, randomized, controlled, observer-blinded, multicenter 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.

Methods

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), as measured by local reactions, systemic events, adverse events (AEs), serious adverse events (SAEs), newly diagnosed chronic medical conditions (NDCMCs), medically attended AEs (MAEs), and immediate AEs in healthy subjects aged ≥24 months to <4 years and in healthy subjects aged ≥4 years to <10 years at study entry, and in the combined age stratum.

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.

Study design

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 1 below for details.

Table 1. 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 population /Sample size

Approximately 400 subjects were planned to be randomly assigned to one of the two groups in a 3:1 ratio.

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.
- Contraindication to vaccination with any HAV vaccine or known latex allergy, or a previous anaphylactic reaction to any vaccine or vaccine-related component, or with a contraindication to intramuscular injection.
- 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.
- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may have increased the risk associated with study participation or investigational product administration or may have interfered with the interpretation of study results and, in the judgment of the investigator, would have made the subject inappropriate for entry into this study.

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.

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 titer ≥ lower limit of quantitation (LLOQ) 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 titer ≥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 titer ≥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.

Furthermore there were several exploratory Analyses and endpoints, which are not discussed in the P46 AR [*only referred to if relevant*]

Safety: There were up to 7 analysis intervals that were used for AEs, SAEs, MAEs, and NDCMCs: within 30 days after Vaccination 1, within 30 days after Vaccination 2, within 30 days after Vaccination 3, within 30 days after any vaccination, during the vaccination phase (from the first study vaccination through 1 month after the last study vaccination), during the follow up phase (from 1 month after the last study vaccination through 6 months after the third study vaccination), and throughout the study (from the first study vaccination through 6 months after the third study vaccination). There were 4 analysis intervals for immediate AEs (AEs occurring within 30 minutes after investigational product administration): Vaccination 1, Vaccination 2, Vaccination 3, and any vaccination.

- Percentage of subjects reporting local reactions (pain, redness, and swelling) and by severity after each vaccination visit.
- Percentage of subjects reporting systemic events (fever, vomiting, diarrhoea, headache, fatigue, muscle pain other than muscle pain at any injection site, and joint pain) and by severity after each vaccination visit.
- Percentage of subjects reporting the use of antipyretic medication after each vaccination visit.
- Percentage of subjects with at least 1 SAE during the 30 days after each vaccination, the 30 days after any vaccination, during the vaccination phase (from the first study vaccination through 1 month after the last study vaccination), during the follow-up phase (from 1 month after the last study vaccination through 6 months after the third study vaccination), and throughout the study period (from the first study vaccination through 6 months after the third study vaccination).
- Percentage of subjects with at least 1 MAE occurring during the 30 days after each vaccination, the 30 days after any vaccination, during the vaccination phase, during the follow-up phase, and throughout the study period.
- Percentage of subjects with at least 1 NDCMC occurring during the 30 days after each vaccination, the 30 days after any vaccination, during the vaccination phase, during the follow-up phase, and throughout the study period.
- Percentage of subjects with at least 1 AE occurring during the 30 days after each vaccination, the 30 days after any vaccination, and during the vaccination phase.
- Percentage of subjects reporting at least 1 immediate AE after each vaccination.
- For subjects at school, days of school missed because of AEs during the vaccination phase (Visit 1 through Visit 6).

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 titer (GMTs) on hSBA results were also summarized with 95% CIs.

The following analysis populations were defined:

- Evaluable immunogenicity population (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 titer ≥ 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.

Results

Recruitment / Number analysed

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.

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.

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 15 below.

Table 15. 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

Immunogenicity results

Primary and Secondary Endpoints

The proportion of subjects in each age stratum with an hSBA titer ≥LLOQ for each of the 4 primary MnB test strains is presented in Table 16 for the evaluable immunogenicity population at different timepoints.

Table 16. Subjects With hSBA Titer ≥ LLOQ for Primary Strains – Evaluable Immunogenicity Population

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]
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 titer ≥ 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 Titer ≥ LLOQ 6 Months After Third Vaccination

In general, there was a decline in the proportion of subjects with an hSBA titer ≥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 titer ≥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 titer ≥ 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 17 provides hSBA GMTs for the 4 primary MnB strains for the evaluable immunogenicity population.

Table 17. 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 Titers

Subjects who achieved an hSBA titer ≥1:4 and ≥1:16 are described below. An hSBA titer of ≥1:4 is widely recognized as the correlate of protection against invasive meningococcal disease (IMD); however, a more conservative hSBA titer of ≥1:16 has been considered a level indicative of a 4-fold vaccine effect for subjects seronegative before vaccination (i.e. fourfold increase in titres for those seronegative at baseline).

The proportion of subjects aged ≥24 months to <4 years, and ≥4 years to <10 years, in Group 1 with an hSBA titer ≥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 titer ≥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 titer ≥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 titer ≥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 titer ≥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 titer ≥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 titers 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 titer ≥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 titer ≥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).

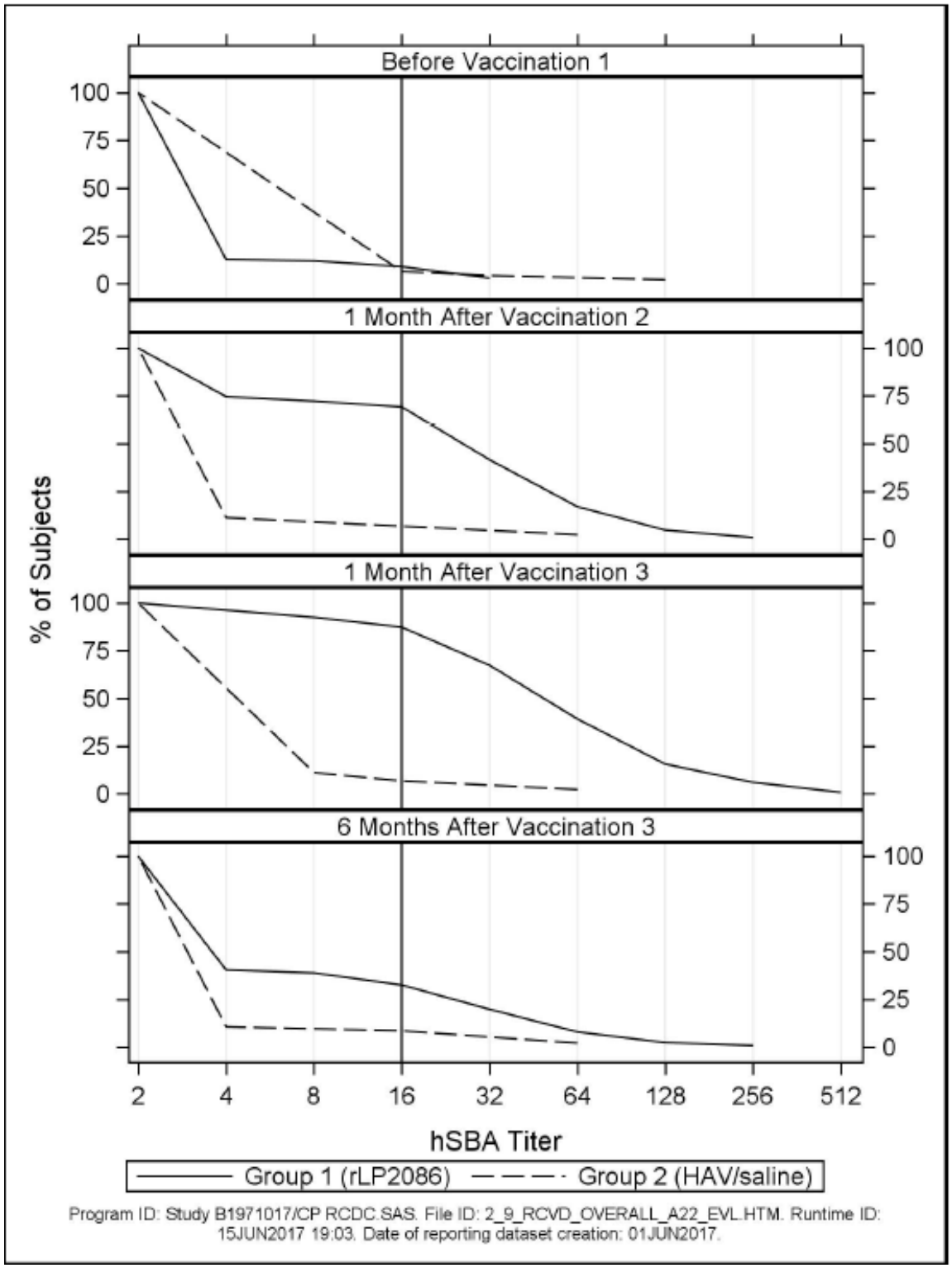
For Group 1 subjects aged ≥24 months to <4 years and aged ≥4 years to <10 years, from 1 month after the third vaccination to 6 months after the third vaccination, the proportion of subjects with an hSBA titer ≥1:16 decreased from 83.8% to 19.0% and 91.0% to 46.0%, respectively, for PMB80 (A22); 100.0% 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 titer ≥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).

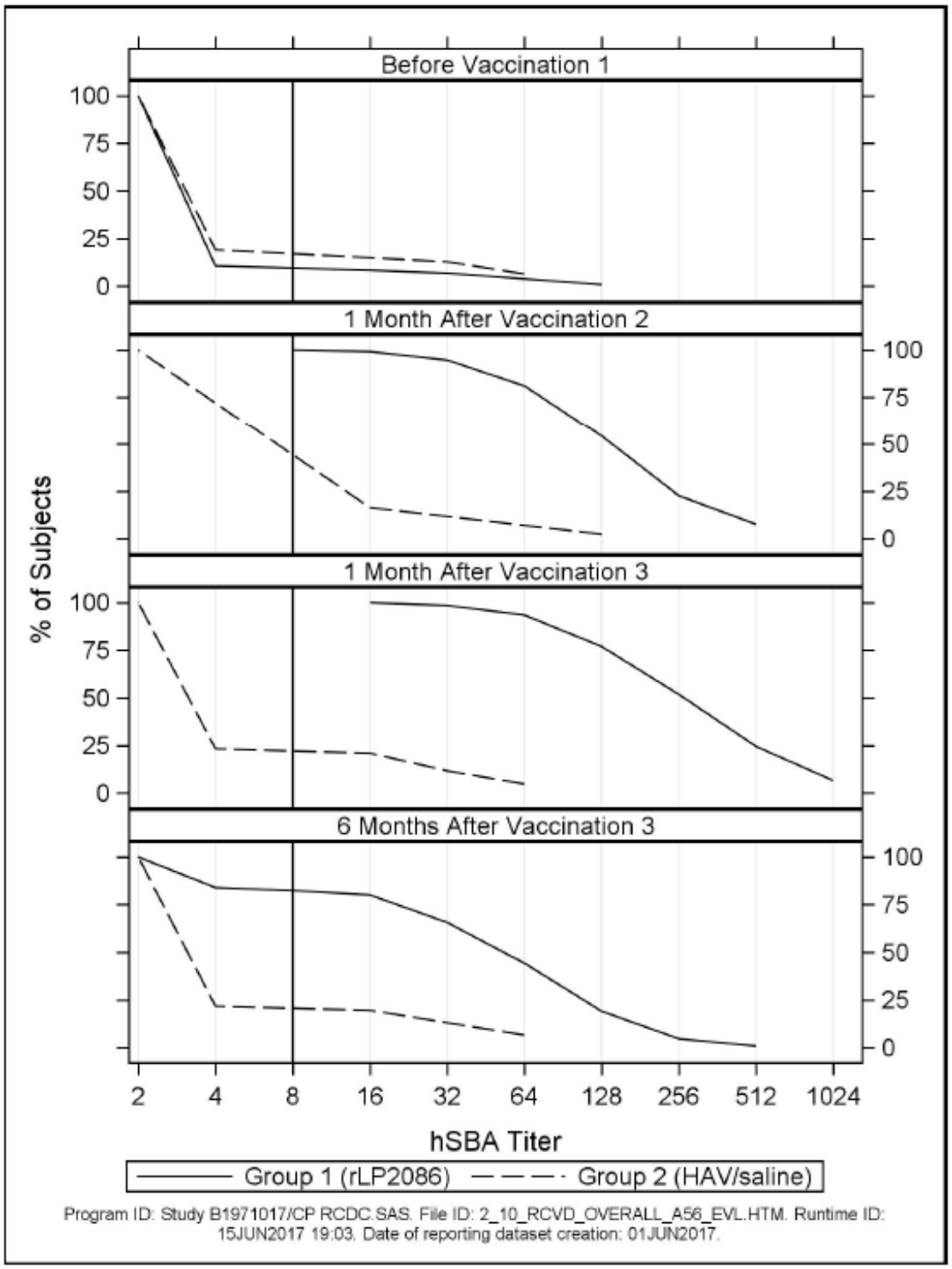
Reverse Cumulative Distribution Curves

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.

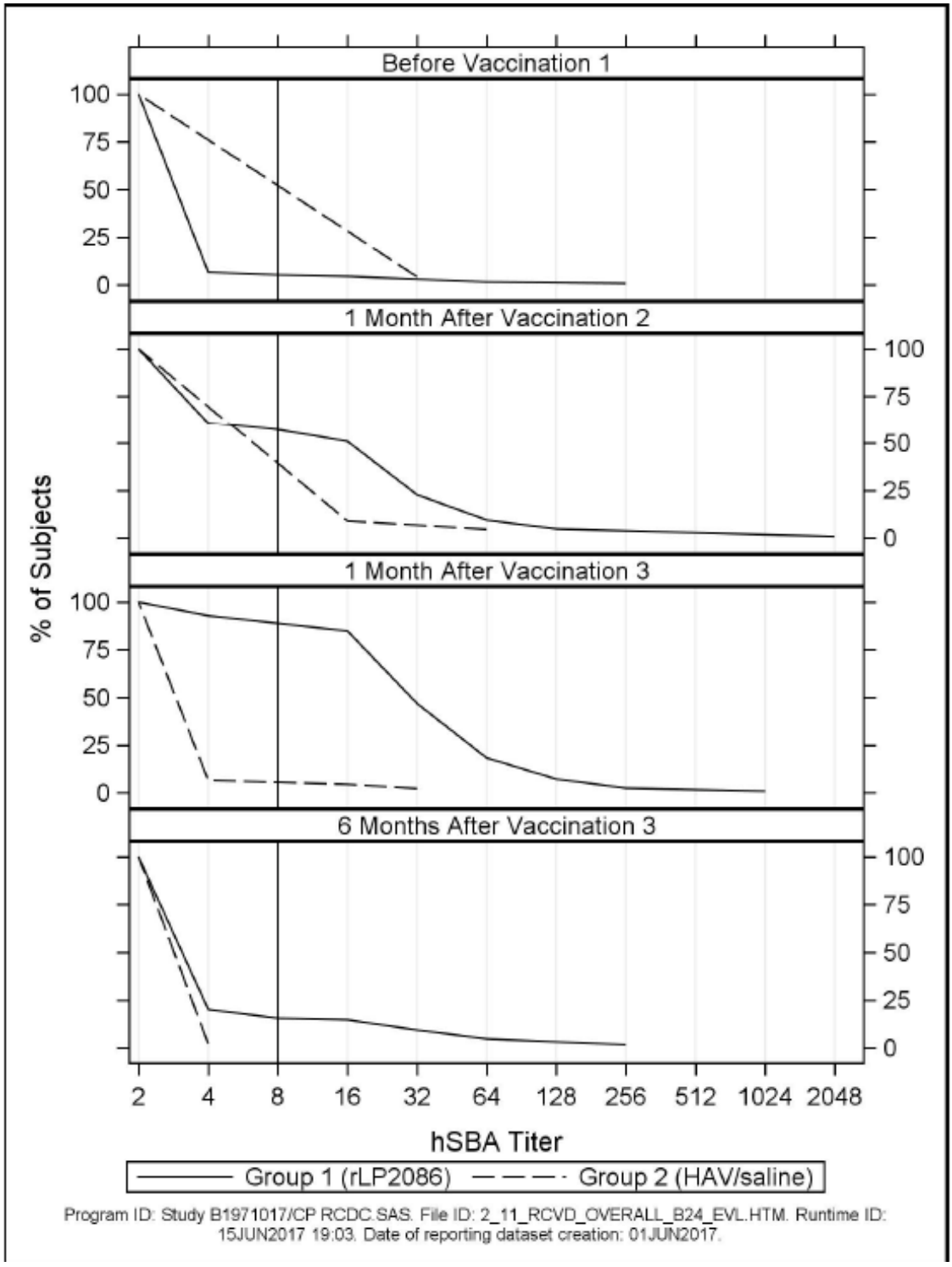
Reverse Cumulative Distribution Curves PMB80 (A22) – Age Strata: ≥24 Months to <10 Years – Evaluable Immunogenicity Population



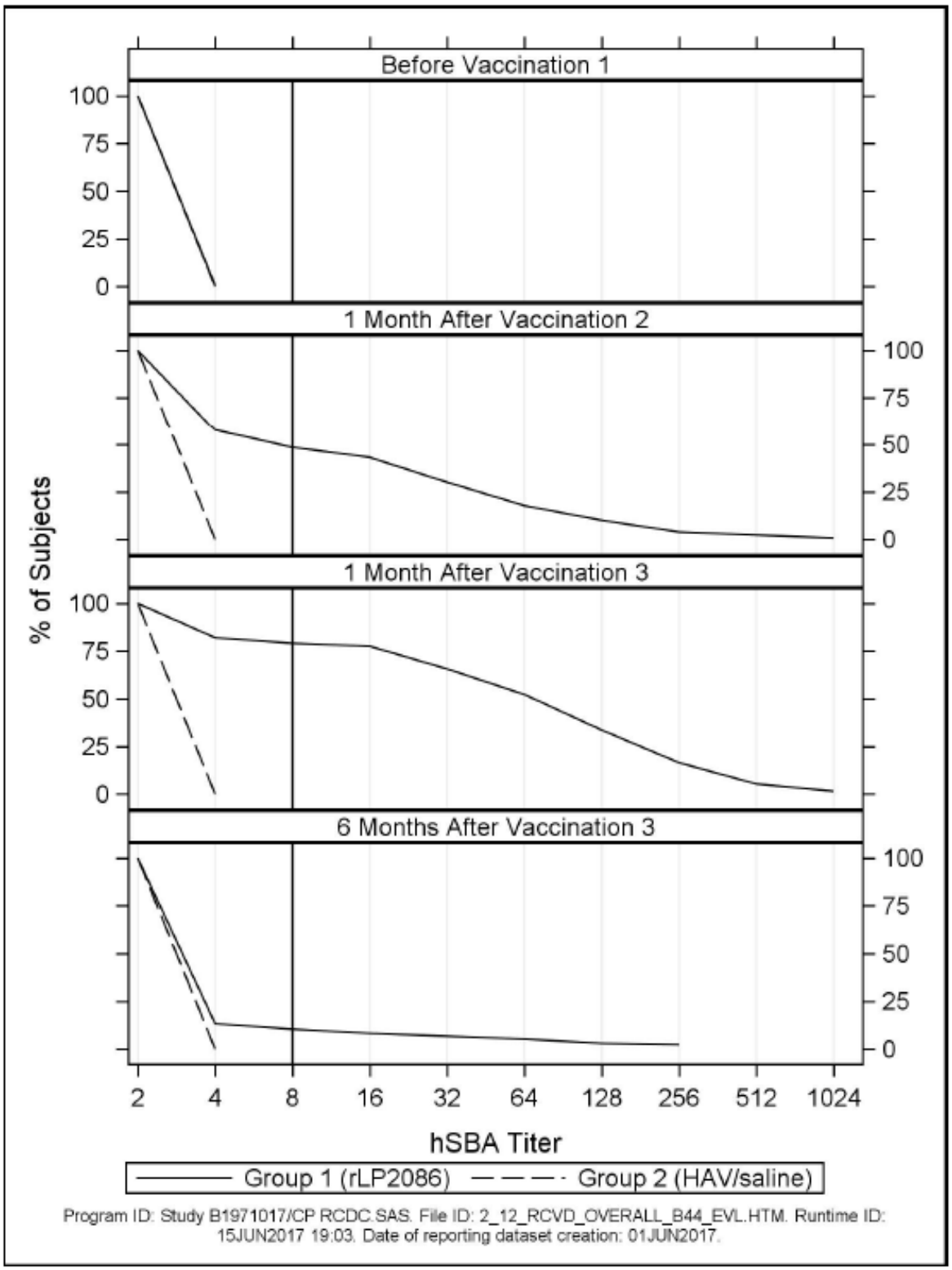
Reverse Cumulative Distribution Curves PMB2001 (A56) – Age Strata: ≥24 Months to <10 Years – Evaluable Immunogenicity Population



Reverse Cumulative Distribution Curves, PMB2948 (B24) – Age Strata: ≥24 Months to <10 Years – Evaluable Immunogenicity Population



Reverse Cumulative Distribution Curves, PMB2707 (B44) – Age Strata: ≥24 Months to <10 Years – Evaluable Immunogenicity Population



Safety results

Local Reactogenicity

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.

	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 reactogenicity

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).

	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. There were no cases of severity increase with potentiation reported 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.

AEs, including SAEs

For the combined age stratum, the percentages of subjects with AEs occurring within 30 days of each vaccination or after any vaccination were equivalent between bivalent rLP2086 and HAV/saline recipients, with overall rates during the vaccination phase of 62.6% and 63.2%, respectively. AEs assessed as related by the investigators were infrequent, and the differences in the percentages of subjects with related AEs were not substantial between the bivalent rLP2086 and HAV/saline groups after any vaccination for the younger and older age strata (2.4% vs 0.0% and 2.4% vs 1.9%, respectively). 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.

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.

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.

Assessor's comments

According to the narrative of the safety related subject withdrawal in relation to the hip synovitis, the subject received the second dose of rLP2086 on 18 March 2016 and the synovitis started on 19 March 2016. The transient synovitis of the hip was deemed related to vaccination based on the temporal relationship to vaccination and the fact that the subject was in good health prior to the second dose. The synovitis was resolved on 31 March 2016. The subject required ER treatment, hence the event being considered serious.

There were 2 additional cases of synovitis 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.

There were two cases of transient hip synovitis occurred close to vaccination in 400 subjects. Transient 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]. [Confidential information deleted]

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.

2.3.3. Discussion on clinical aspects

Immunogenicity Discussion

Immunogenicity results from this Phase 2 study of a 3-dose regimen (0-, 2-, and 6-month schedule) of bivalent rLP2086 given to toddlers and children aged ≥24 months to <10 years are consistent with previous studies in adolescents and young adults.

Immunogenicity responses to bivalent rLP2086 vaccination were measured in validated hSBAs using 4 primary MnB test strains, each expressing fHBP variants heterologous to the vaccine component antigens, as has been applied throughout the dossier submitted for the initial marketing authorization.

Based on an hSBA titer ≥ LLOQ for the 4 primary MnB test strains 1 month after Vaccination 3, the toddlers and children participating in this study had largely similar immune responses compared to adolescents (10 years to <19 years) participating in Study B1971009, with proportions of subjects achieving an hSBA titer ≥ LLOQ after the third vaccination (0-, 2-, 6-month schedule) ranging from 79.1% to 100% in this study and 87.1% to 99.5% in Study B1971009. Of note, study B1971009 had a much higher proportion of adolescent subjects with a prevaccination hSBA titer ≥ LLOQ compared to the toddlers and children in this study, particularly for the A22 (33.2% vs 9%, respectively) and A56 (27.5% vs 8.3%, respectively) test strains.

Bivalent rLP2086 appears to be immunogenic in the ≥24 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, the low hSBA titers 6 months after Vaccination 3 suggest a steep decline in protection for strains A22, B24 and B44. The proportion of subjects achieving an hSBA titer ≥ 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 titer ≥ LLOQ declining from 100% to 82.4% over the same period. Results from study B1971005 would suggest immune persistence being better in adolescents. In study B1971005, where the median age was 14 years, the proportion of subjects achieving an hSBA titer ≥ 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 yrs, which showed better persistence still at 12 months after the third dose. No 6 month data were available for comparison.

The MAH suggests that differences between subjects aged ≥24 months to <10 years and older age groups may be partially attributable to the proportion of subjects with a baseline titer ≥ LLOQ, which were as high as 27.5% (A56) and 33.2% (A22) in Study B1971009, and 7.4% to 13.4% for subfamily A strains in Study B1971005. *[Confidential information deleted]*

As the MAH suggests, post-booster response and persistence studies are therefore warranted among individuals who received their primary series of bivalent rLP2086 as toddlers and children to provide further insights into the utility of a booster dose in providing protection against IMD through childhood, adolescence and early adulthood. *[Confidential information deleted]* At this time no dosing recommendation can be made for children aged 24 months to 10 years.

Discussion on the safety

Bivalent rLP2086 was well tolerated by toddlers and children aged ≥24 months to <10 years. The data show that bivalent rLP2086 is a reactogenic vaccine, with a high proportion of subjects reporting local reactions.

The most frequently reported local reaction was pain at the injection site. The percentage of subjects receiving bivalent rLP2086 reporting injection site pain was lower in this study compared to adolescents receiving bivalent rLP2086 in Study B1971009, 84.4% versus 92.6%, respectively. 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 and swelling were more prominent among the younger subjects in this study than among the adolescents in Study B1971009, 60.2% vs 24.1% and 46.6% vs 27.4%, respectively.

Considering the rates of systemic reactions in subjects included in this study 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.

Fever was more common in toddlers 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. Within this study, 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, 9.7% of subjects aged ≥24months to <4 years reported fever ≥39.0°C, 1.4% reported fever >40°C. For children aged ≥4 to <10 years this was 3.3% and 0% respectively.

Injection site redness and swelling, fever, and use of antipyretics occurred more frequently among toddlers and children in this study compared to adolescents and young adults in previous studies.

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, and the percentage of subjects reporting AEs was only modestly higher (44.2%) 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 toddlers and children aged ≥24 months to <10 years.

The percentage of bivalent rLP2086 recipients reporting SAEs was 1.7%, which is consistent with what has been observed in the 8 previously conducted controlled clinical trials involving 13,275 bivalent rLP2086 recipients and 5,501 controls, for which the SAE rates were 1.6% and 1.9%, respectively. There was 1 related SAE (0.3%) reported in this study - 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 nonserious 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]. *[Confidential information deleted]*

3. Rapporteur's overall conclusion and recommendation

The data from study B1971017 demonstrate that following a 0,2,6 month schedule, one month after the third dose an immune response that can be considered to be protective is achieved against relevant test strains in the large majority of vaccinated subjects aged ≥24 months to 10 years. Immune persistence is however very poor against three of the four test strains, and appears poorer than has been observed for older individuals ≥10 years of age.

Post-booster response and persistence studies are therefore warranted among individuals who received their primary series of bivalent rLP2086 as toddlers and children to provide further insights into the utility of a booster dose in providing protection against IMD through childhood, adolescence and early adulthood. *[Confidential information deleted]*

Considering the safety, the data show that as in adolescents and adults the vaccine is fairly reactogenic with a relatively high proportion of subjects reporting pain and other local and systemic reactions. Likewise, the use of antipyretics to self-treat symptoms during the 7 days following vaccination was relatively high. *[Confidential information deleted]*

According to the PIP this is the only planned study in this age group, subjects age ≥24 months to <10 years. The data are considered of relevance to prescribers, even though the applicant is not applying for an extension of indication to include this age group. **Therefore the MAH is requested to update the sections 4.2 and 5.1 of the SmPC based on the available data.**

☒ **Fulfilled:**

No further action required, however further data are expected in the context of a variation prior to any conclusion on product information amendments are made. The MAH should submit this variation application by 30 September 2018.